PB90-143025

EBDC Special Review: Technical Support Document 2/3

(U.S.) Environmental Protection Agency, Washington, DC

Dec 89

U.S. Department of Commerce
National Technical Information Service
NTIS

BIBLIOGRAPHIC INFORMATION

PB90-143025

Report Nos: EPA/540/09-90/077

Title: EBDC Special Review: Technical Support Document 273.

Date: Dec 89

Performing Organization: Environmental Protection Agency, Washington, DC. Office of Pesticides and Toxic Substances.

NTIS Field/Group Codes: 68E, 68G, 57U, 57P, 57Y

Price: PC A14/MF A02

Availability: Available from the National Technical Information Service,
Springfield, VA. 22161

Number of Pages: 318p

Keywords: *Pesticides, Exposure, Reviews, Public health, Regulations, Carcinogens, Plants(Botany), Farm crops, Industrial plants, Fungicides, Toxicity, Thyroid diseases, *Risk assessment, *Carbamic acid/ethylene-bis(dithio), *Imidazolidine thione, Occupational safety and health, Environmental effects.

Abstract: The Environmental Protection Agency is examining the ethylene bisdithiocarbamates (maneb, mancozeb, metiram, nabam and zineb) because of carcinogenic, developmental and thyroid effects caused by ethylenethiourea (ETU), a common contaminant, metabolite and degradation product of these pesticides. Available data has led the Agency to conclude that the continued registration of EBDC products for use on certain food crops, commercial ornamentals and home garden sites and in some industrial uses would result in unreasonable adverse effects to humans. In determining which uses to cancel, the Agency considered the aggregate risks posed by the EBDCs and ETU, the extent to which registered uses are being supported by registrants and, where appropriate, the risks and benefits of individual uses.

PB90-148925

United States
Environmental Protection
Agency

Office of
Pesticides and Toxic Substances
Washington, DC 20460

December 1989

Pesticides

540/09-90-077

EPA EBDC

SPECIAL REVIEW

TECHNICAL SUPPORT

DOCUMENT

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL INFORMATION SERVICE
SPRINGFIELD, VA 22161

EBDC
TECHNICAL SUPPORT DOCUMENT
POSITION DOCUMENT 2/3

THE ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES AND TOXIC SUBSTANCES
OFFICE OF PESTICIDE PROGRAMS
SPECIAL REVIEW AND REREGISTRATION DIVISION
SPECIAL REVIEW BRANCH
401 M STREET, S.W.
WASHINGTON, D.C. 20460

EXECUTIVE SUMMARY

On July 17, 1987, (52 FR 27172) EPA initiated a Special Review of the ethylene bisdithiocarbamate (EBDC) pesticides. There are five EBDC active ingredients currently registered: mancozeb, maneb, metiram, nabam, and zineb. All registrations of a sixth EBDC, amobam, have been cancelled. The initiation of the Special Review was based on the Agency's determination that exposure to ethylenethiourea (ETU), a common contaminant, metabolite, and degradation product of these pesticides, may pose carcinogenic risks to humans from dietary exposure and risk of cancer, developmental and thyroid effects to mixers, loaders, and applicators (including homeowners). The Agency determined that the risk criteria, as described in 40 CFR 154.7(a)(2) and 154.7(a)(6), were met or exceeded by use of EBDC pesticides. The Agency at the same time solicited information to support its assessment of the benefits of the EBDCs.

Maneb, mancozeb, metiram and zineb are registered for use to prevent damage by fungi to a wide variety of food and ornamental crops as well as being used as seed and seed piece treatments, as soil treatments, and for home gardens. Approximately 12 to 18 million pounds of all EBDCs are used in the U.S. each year, primarily on potatoes, apples, cucurbits, tomatoes, onions, sweet corn and small grains.

In 1986, the zineb technical registrants cancelled their registrations, but one end use formulator agreed to support a number of uses. All uses of zineb were suspended by the Agency in July 1988 when that formulator failed to submit data required under FIFRA section 3(c)(2)(B). In July 1989 that formulator notified the Agency that he wanted to voluntarily cancel his registrations and the Agency issued a second notice to the remaining formulators in October 1989. At the time the Position Document was issued, no formulators had yet agreed to support zineb registrations.

All nabam agricultural food and feed use registrations have been suspended since 1985. On March 13, 1989, the registrant of the suspended food uses (Rohm and Haas Company) requested that the Agency cancel all the suspended food uses of nabam. The Agency's acceptance of this request is imminent. Nabam is currently registered as a fungicide on ornamental plants and as a biocide in industrial cooling tower water systems, oil well drilling fluids and pulp and paper mills. Registrants holding nabam registrations on industrial sites requested voluntary cancellation of sugar beet and sugarcane transport and flume water nabam uses in 1987, but have retained the use of nabam in sugar mill grinding, crusher or diffuser systems.

As part of the Special Review process, the Agency evaluates the risks and benefits associated with the uses of a pesticide and then proposes any regulatory actions necessary to ensure that use of the pesticide does not result in unreasonable adverse effects. In determining which uses to cancel, the Agency considered the aggregate risks posed by the EBDCs, the extent to which registered uses are being supported by registrants and, where appropriate, the risks and benefits of individual uses.

ETU has been classified by the Agency as a Group B_2 carcinogen (probable human carcinogen) based on evidence that it induced an increased incidence of thyroid follicular cell adenomas and adenocarcinomas in rats and thyroid and liver tumors in three strains of mice. The classification as a Group B_2 carcinogen is also supported by structure-activity relationships, since several other thyroid inhibitors which are structurally related to ETU (e.g., thiouracil and thiourea) have also been found to induce hepatomas and/or thyroid tumors in rodents. Available studies also show ETU demonstrated the ability to cause developmental effects (hydrocephalus) in rats and thyroid effects (hyperplasia) in rats, mice, and monkeys.

The Agency's assessment of ETU's potential carcinogenic, developmental, and thyroid risks in the PD 1 was based on a limited exposure data base. Estimates of carcinogenic risks were based on mancozeb (and ETU) residue and exposure data. Developmental and thyroid risk estimates were based on mancozeb (and ETU) and surrogate exposure studies and an assumption of 100 percent dermal absorption.

Since issuance of the Notice of Initiation of a Special Review, the Agency has received additional toxicity and exposure data on the individual EBDCs and an ETU. These data have been used to refine the risk estimates presented in this document. Due to the fact that all nabam agricultural food and feed uses are suspended and are in the process of being voluntarily cancelled, the Agency has not required any additional crop residue data on nabam.

From an assessment of all available data, the Agency estimates a 95 percent upper-bound ETU carcinogenic dietary risk of 4×10^{-4} to the general public from exposure to ETU from consumption of food crops treated with maneb, mancozeb and metiram. This risk estimate would increase if the uses of zineb also were allowed to continue. This estimated carcinogenic dietary risk is based on field residue studies for maneb, mancozeb, and metiram where the parent compound (EBDC) and ETU were measured, and took into consideration percent of crop treated estimates. Due to the fact that analytical methods are unable to determine the source of the ETU contribution from individual EBDC chemicals (more than one EBDC is registered for use on some crops) and that currently available analytical methods cannot distinguish among the various EBDC fungicides unless the identity of the pesticide used is known, carcinogenic dietary risk is considered in this document as the total ETU contribution to individual crops. ETU risk estimates for individual crops treated with EBDCs range from 10^{-10} (crenshaw melons) to 10^{-4} (apples). See Table II-17.

Developmental dietary margins-of-safety/margins-of-exposure (MOSs/MOEs) were calculated for each EBDC parent compound. All developmental dietary MOSs/MOEs were over 600. See Table II-18.

Carcinogenic mixer/loader/applicator (M/L/A) risks range from 10^{-3} to 10^{-7}. For commercial agriculture and industrial workers with the incorporation of protective clothing (coveralls over shirts and pants, chemical resistant gloves, shoes, socks, and goggles or a face shield), only one estimate of carcinogenic M/L/A risks remains at 10^{-3}: commercial applicators using maneb on ornamentals. For some homeowner uses (i.e., maneb on homeowner vegetables, ornamentals, fruit trees, and turf sites and mancozeb on homeowner fruit trees and turf sites), no practical additional protective clothing requirements reduce estimated risks to reasonable levels (estimated risks exceeding 10^{-6} and low benefits). Consequently, these homeowner uses are proposed for cancellation.

Developmental (acute exposure) and thyroid effects (chronic exposure) MOSs/MOEs were estimated for agricultural workers, commercial applicators, homeowners, and industrial workers who may be exposed to ETU from the application of all EBDC pesticide products. With incorporation of protective clothing, several MOSs/MOEs still remained below 100 for developmental toxicity (maneb on homeowner turf) and thyroid effects (maneb on grapes and commercial ornamentals and nabam in sugar and paper mills). See Table II-20. Due to the fact that the Agency has M/L/A exposure data that enable it to estimate ETU M/L/A exposure contribution from individual EBDC parent compounds, M/L/A risks are given for each EBDC pesticide.

The benefits of the EBDCs were assessed in terms of the economic impacts which would result if the chemicals were fully withdrawn from the market for the particular uses and users were forced to substitute alternatives. Benefits in this document are calculated in terms of producer impacts and efficiency impacts. Producer impacts are increased costs for growers. Efficiency impacts are defined as society costs, or the loss to society of the dollar value of goods and services no longer available as a result of the action. Efficiency impacts include costs to growers, as well as to consumers and others. Producer impacts are provided for crops where it is assumed growers will not be able to pass on the increased costs of production. Efficiency impacts are provided where it is assumed that impacts would occur at more than one level of the production/distribution chain. For some of these crops, such as tomatoes, higher production costs could be offset by higher yields gained through use of alternative pesticides. Other factors considered were the efficacy, phytotoxicity, potential for fungal resistance and cost of each alternative. Crops for which there are no viable registered alternatives are: asparagus, corn (field and sweet), cranberries, endive, lettuce, and spinach. Two of these crops have estimated individual ETU carcinogenic risks of greater than 10^{-7} (lettuce and spinach). The estimated annual benefit from all dietary uses is $46 to $75 million in producer impacts and $90 to $305 million in efficiency impacts if use on all 55 crops was cancelled. Estimated annual benefit from non-food agricultural and industrial uses is $5 to $15 million in producer impacts.

The Agency examined a range of options to reduce the unreasonable carcinogenic, developmental and thyroid effects of the EBDCs to the general public from consumption of foods treated with these pesticides and/or to applicators, mixers, and loaders who use these pesticides. For dietary exposure, these included extending preharvest intervals and modifying application practices such as reducing application rates. However, the available information (including information submitted in response to the PD 1) is insufficient to assess the feasibility of these measures. The Agency urges interested parties to provide data or other analyses to demonstrate the impact of such measures as reductions in application rates or frequencies or increases in preharvest intervals, as ways of reducing exposure from particular crops. EPA will consider this information when the Agency develops its final decision concerning the EBDCs. EPA urges interested parties to seek technical guidance from the Agency early on so that the most useful, valid data are developed.

For mixers, loaders, and applicators of EBDCs, the Agency considered requiring additional protective clothing to that specified in the Registration Standards for maneb, mancozeb, metiram and nabam (coveralls for mixer/loaders and coveralls and gloves for applicators) for agricultural workers and commercial applicators. Based on surrogate data, these additional measures are estimated to reduce exposure in excess of 40 percent, depending on the protective measures utilized. The Agency did not consider it practical to require the above-mentioned additional protective clothing for homeowners.

Based on its analysis of the risks and benefits, the Agency proposes the following regulatory actions:

A. Food Crop Uses

In determining the appropriate regulatory action, the Agency considered (1) the risks posed by the EBDCs from lifetime dietary exposure, (2) the estimated excess lifetime cancer risks resulting from exposure during the time it will take to complete the Special Review process, (3) the extent to which registered uses are supported by registrants, (4) the risks and benefits of individual uses, where appropriate, (5) the risks associated with alternative fungicides that likely would be used if EBDC registrations are cancelled, and (6) the likelihood that additional data and information might result in a different final decision.

Based on its analysis, EPA has determined that dietary risks from a lifetime of exposure are unreasonable, and therefore, the Agency proposes to cancel many of the food uses of the EBDCs. At the same time, EPA is convinced that risks from exposure during the time needed to complete the Special Review process are negligible since registrants have acted to sharply restrict pesticide usage beginning in 1990. (See Chapter V.) Thus, more severe action is not necessary to protect the American public in the short-run.

To ensure that risks from short-term exposure are negligible, the Agency will proceed with certain actions to reduce exposure. These actions involve deleting uses from certain registrant labels pursuant to requests by those registrants and tolerance revocations to reduce exposure on both domestic and imported crops. In addition, EPA should be receiving monitoring data from registrants which will provide data on actual residue levels; the Agency will take further action if estimated risks during the pendency of its deliberation are unacceptable.

The Agency proposes the cancellation of 45 food uses of maneb, mancozeb and metiram and all uses of zineb. Forty-two uses of maneb, mancozeb and metiram and all the uses of zineb are being cancelled due to unacceptably high risk of ETU and the present lack of support for these uses by registrants. The remaining three uses of maneb, mancozeb and metiram are being proposed for cancellation because the risks of the individual uses outweigh the benefits.

All zineb uses are currently suspended and the only technical registrant has requested voluntary cancellation of its registrations. In addition, on September 6, 1989, the four major registrants of maneb, mancozeb and metiram requested EPA to delete 42 of 55 uses from their registrations. They planned to retain 13 uses. Their action would decrease risk from 4×10^{-4}

to 2 x 10^{-5}. The 13 uses proposed to be retained by these registrants are almonds, asparagus, bananas, cranberries, figs, grapes, onions, peanuts, potatoes, sugar beets, sweet corn, tomatoes and wheat. By the registrants' action, maneb would be registered for use on almonds, bananas, potatoes, sugar beets and sweet corn; mancozeb would be registered for use on asparagus, bananas, cranberries, figs, grapes, onions, peanuts, potatoes, sugar beets, sweet corn, tomatoes and wheat; and metiram would be registered for use on potatoes. The estimated cumulative benefit from these 13 crops is $14 to $27 million in producer impacts.

This voluntary action by registrants was taken in an effort to reduce possible dietary risks associated with consumption of EBDC-treated commodities. Once the registrants' action becomes final, the deleted uses cannot be reinstated until such time as the registrants apply to reinstate these uses and the Agency determines the risks associated with these uses are found to be acceptable.

The four technical registrants of maneb, mancozeb and metiram control a significant share of the EBDC market but not all of it. However, EPA believes that the action of these registrants has altered the market sufficiently that it is appropriate to consider that only the use of maneb, mancozeb and metiram on 13 crops are likely to remain.

EPA considered the registrants' action and concluded that, while it constituted a major step to reduce dietary risk, it did not go far enough to reduce risks to acceptable levels.

Therefore, EPA proposes to retain the use of maneb, mancozeb and metiram on ten of the 13 crops (almonds, asparagus, cranberries, figs, grapes, onions, peanuts, sugar beets, sweet corn and wheat) and proposes to cancel use on three crops three (potatoes, tomatoes and bananas). The estimated risks resulting from the ten retained crops would be 3×10^{-6} and estimated benefits would be $13 to $26 million in producer impacts.

B. Tolerances

Within 90 days of the issuance of this document, the Agency intends to propose tolerance revocations for the 45 food uses of maneb, mancozeb and metiram and all (58) food uses of zineb proposed for cancellation in this Preliminary Determination. The Agency presently intends to finalize the tolerance actions, reflecting consideration of public comments, when all products for particular uses are voluntarily cancelled, or the Agency issues the Final Determination, whichever occurs earlier. In issuing final rules to revoke tolerances, the Agency will set tolerance expiration dates which take into consideration any crops which were treated legally before the effective date of the cancellation. Tolerances for retained uses will be reevaluated once the Agency receives metabolism and residue data required under the EBDC Comprehensive Data Call-Ins and Registration Standards. Any necessary adjustments to raise or lower existing tolerances will be proposed at that time.

C. Non-Industrial Uses

The Agency proposes a label language requirement that commercial agricultural workers (M/L/A) applying EBDC pesticides wear coveralls over long-sleeved shirt and long pants, chemical-resistant gloves, shoes, socks, and goggles or a face shield. Additionally, during mixing and loading, a chemical-resistant apron must be worn. With incorporation of the above-mentioned protective clothing requirements, MOSs/MOEs for workers using EBDC products on agricultural sites would all increase above 100 except for maneb uses on grapes and ornamentals which are proposed for cancellation because EPA has determined that risks exceed benefits.

The Agency estimates that the cost of the above protective clothing would range from $0.75 to $1.5 million if every commercial agricultural user of EBDC pesticides needed to buy the protective equipment. However, the Agency believes the costs of this requirement would actually be much lower because most growers already own such equipment as it is required for use when applying a number of other agricultural chemicals.

The Agency proposes a label language requirement establishing an interim reentry interval of 24 hours for all EBDC products used on agricultural sites. This interim reentry interval will remain in effect until dislodgeable foliar residue data (showing EBDC and ETU exposure to agricultural workers reentering treated fields for the purposes of hand harvesting, pruning, weeding, etc.) required in the EBDC Registration

Standards and as required in the March 1989 EBDC Data Call-In Notice are submitted and evaluated. These data are due to be submitted in July 1990. The Agency believes that there would be little if any economic impact from this requirement.

The Agency did not consider that additional protective clothing requirements for homeowners would be a viable means of reducing risks because the Agency believes that homeowners will not go to the expense of purchasing or wearing protective clothing. Therefore, EPA proposes to cancel the use of maneb on turf by homeowners where MOSs/MOEs are under 100, and risks outweigh benefits.

In addition, because millions of households have gardens and many more have lawns which could be treated, the Agency is concerned about estimated cancer risks which exceed 10^{-6} for homeowners applying EBDCs. EPA believes such risks exceed the benefits of use. Homeowner sites which have estimated risks exceeding 10^{-6} are: (1) mancozeb on fruit trees and turf and (2) maneb on vegetables, ornamentals, fruit trees and turf. See Table II-19. Little or no economic impact is expected because home gardeners can switch from maneb to mancozeb for vegetables and ornamentals and can use captan on fruit trees instead of EBDCs. The Agency estimates that less than one percent of residential lawns are treated with EBDCs and any impact would be negligible. Therefore, EPA proposes to cancel homeowner use of mancozeb on fruit trees and turf, and homeowner use of maneb on vegetables, ornamentals, fruit trees and turf.

D. Industrial Uses

The Agency proposes a label language requirement that all industrial workers (M/L/A) applying EBDC pesticides wear coveralls over long-sleeved shirt and long pants, chemical-resistant gloves, shoes, socks, and goggles or a face shield. Additionally, during mixing and loading, a chemical-resistant apron must be worn. Similar label language already appears on most nabam labels and OSHA requires protective clothing when applying hazardous chemicals under 29 CFR §1910.132; therefore, the Agency believes there would be minimal costs resulting from this requirement.

The Agency proposes cancellation of nabam use in paper mills and sugar mills based on thyroid MOSs/MOEs below 100 due to occupational exposure after incorporation of protective clothing requirements listed above. EPA has determined that risks outweigh benefits in these cases. If nabam's use were cancelled, the cost to the paper industry would increase by $700,000. There are three alternatives for nabam's use in sugar mills. The most viable alternative (Busan) possibly would increase production costs between $400,000 to 500,000 if it replaced nabam.

E. Schedule for PD-4

Due to the assumptions surrounding dietary and mixer/loader/applicator risks, the Agency has required additional data through FIFRA section 3(c)(2)(B) to further refine risk estimates. The Agency plans to issue the PD 4 in the spring of

1991 to allow review and consideration of additional data, which the Agency currently believes could result in a more refined risk/benefit assessment of the EBDCs and ETU. However, if new data or information demonstrate a need to take more immediate action, the Agency will do so.

ACKNOWLEDGEMENTS

EBDC Project Team

Office of Pesticide Programs Team Members

Valerie M. Bael	Senior Review Manager, SRB
Janet Andersen	Section Chief, SRB
Karis L. North	Review Manager, SRB
Gary L. Ballard	Supervisory Economist, BEAD
Christen R. Bashor	Occupational Safety Specialist, OSB
Leung Chang	Chemist, HED
Kenneth W. Clark	Agronomist, EEB
Henry Craven	Biologist, EEB
Kerry Dearfield	Geneticist, HED
Richard P. Dumas	Economist, BEAD
Michael P. Firestone	Chemist, NDEB
Judith W. Hauswirth	Supervisory Chemist, HED
Patrick Holden	Chemist, SACB
Susan V. Hummel	Chemist, DEB
Albin Kocialski	Pharmacologist, HED
Richard N. Lee	Entomologist, EEB
Richard Levy	Senior Statistician, HED
Susan T. Lewis	Environmental Protection Specialist, RD
Curt Lunchick	Chemist, HED
Irving Mauer	Geneticist, HED
E. Neil Pelletier	Plant Pathologist, BEAD
Franklin D. Rubis	Environmental Protection Specialist, RD
Esther C. Saito	Chemist, HED
William Sette	Toxicologist, HED
J. Robert Tomerlin	Plant Pathologist, HED
Linda L. Taylor	Toxicologist, HED
Douglas J. Urban	Supervisory Biologist, EEB
Edward Zager	Supervisory Chemist, DEB

External Office Team Members

Michael Branagan	Analyst, OPPE
Barbara Britton	Analyst, ORD
Philip J. Ross	Attorney, OGC
John Fleucheus	Attorney, OGC
Daniel Helfgott	Environmental Protection Specialist,OCM

TABLE OF CONTENTS

Executive Summary i
Acknowledgements xvi
Listing of Tables xxi
Glossary xxiii

I. INTRODUCTION

A. REGULATORY BACKGROUND

1. The Special Review Process I-1
2. Special Review Actions I-2

B. Organization of this Position Document I-7

C. CHEMICAL BACKGROUND

1. Chemical and Physical Characteristics I-8
2. Registered Uses and Production I-12
3. Tolerances I-19

II. ASSESSMENT OF RISKS AND ANALYSIS OF REBUTTAL COMMENTS

A. EFFECTS OF CONCERN

1. Carcinogenicity II-1

a. Hazard Identification II-2
b. Mutagenicity II-14
c. Non-Genotoxic Tumor Formation II-19
d. Summary of ETU Metabolic and Pharmacokinetic Properties II-21
e. Structure-Activity-Relationship II-24
f. Human Studies II-24
g. Weight-of-Evidence for Carcinogenicity .. II-24
h. Dose Response II-27
i. Determination of Carcinogen Potency Factor (Q_1^*) for Risk Calculations II-28

2. Developmental Effects II-29

3. Thyroid Effects II-31

4. Aquatic Effects II-32

5. Avian Toxicity II-33

6. Ground Water II-34

B. EXPOSURE ANALYSIS

1. Dietary Exposure II-35

   a. Background II-35
   b. Carcinogenicity and Thyroid Effects II-39
   c. Developmental Effects II-60

2. Worker Exposure II-71

   a. Methodology II-71
   b. Agricultural Uses II-73
   c. Commercial ornamentals II-79
   d. Homeowner Lawns and Gardens II-80
   e. Industrial II-86

C. RISK CHARACTERIZATION

1. Dietary II-90

   a. Carcinogenic.................................. II-91
   b. Developmental Toxicity......................... II-94
   c. Thyroid Effects II-99
   d. Conclusions II-100

2. Mixer/loader/applicator II-102

   a. Carcinogenic.................................. II-102
   b. Developmental and Thyroid Effects II-107
   c. Conclusions II-108

D. REBUTTAL ANALYSIS

1. Carcinogenicity.. II-120

2. Mutagenicity II-124

3. Developmental Effects.................................. II-126

4. Thyroid Effects II-127

5. Exposure II-130

6. Other II-139

III. ASSESSMENT OF BENEFITS AND ANALYSIS OF REBUTTAL COMMENTS

A. ASSESSMENT OF BENEFITS

1. Method of Analysis III-1

2. Introduction III-3

3. Food crops III-13

   a. Root/tuber crops III-13
   b. Onions III-20
   c. Leafy vegetables III-22
   d. Cole crops III-30
   e. Peanuts III-33
   f. Peppers III-35
   g. Tomatoes III-36
   h. Curcurbits III-39
   i. Apples III-41
   j. Peaches and Nectarines III-45
   k. Cranberries III-46
   l. Grapes III-47
   m. Bananas III-49
   n. Sweet corn III-51
   o. Small grains III-53
   p. Other crops III-56

4. Seed Treatments III-57

5. Non-food crops III-57

   a. Ornamental plants III-57
   b. Turfgrass III-59

6. Industrial sites III-61

   a. Paper mills III-61
   b. Water cooling systems III-62
   c. Sugar mills III-63
   d. Oil Well Drilling Fluids III-64
   e. Metal Working Coolants III-65

B. ANALYSIS OF REBUTTAL COMMENTS III-66

IV. RISK/BENEFIT ANALYSIS AND REGULATORY OPTIONS

A. INTRODUCTION IV-1

B. RISK CONCLUSIONS IV-1

   1. Carcinogenicity IV-2

   2. Developmental Toxicity IV-3

   3. Thyroid Effects IV-3

   4. Risks from Alternatives IV-3

C. BENEFITS CONCLUSIONS IV-7

D. DEVELOPMENT OF REGULATORY OPTIONS IV-8

1. Measures to Reduce Dietary Exposure IV-10

a. Preharvest interval IV-10
b. Modify Application Practices IV-10

2. Measures to Reduce Exposure to Applicators, Mixer/Loaders and Fieldworkers IV-11

a. Protective Clothing IV-12
b. Reentry Intervals IV-13

3. Measures to Reduce Industrial Worker Exposure IV-14

E. RISK/BENEFIT ANALYSIS OF REGULATORY OPTIONS ... IV-14

1. Option 1: Continuation of Registration Without Changes IV-14

2. Option 2: Continuation of Registrations with Modifications to the Terms and Conditions of Registration IV-15

3. Option 3: Partial Cancellation IV-18

4. Option 4: Cancellation IV-30

V. PROPOSED REGULATORY OPTIONS V-1

A. FOOD CROP USES V-2

B. TOLERANCES V-8

C. NON-INDUSTRIAL USES V-9

D. INDUSTRIAL USES V-11

VI. REFERENCES VI-1

List of Tables

Table I-1: EBDC Nomenclature
Table I-2: Chemical and Physical Properties of EBDCs
Table I-3: EBDC Registered Sites
Table II-1: Liver Tumors in ETU-Treated Mice
Table II-2: Tumor Induction in Rats by ETU
Table II-3: Histopathology Data from Graham et al. (1975)
Table II-4: Mutagenicity of ETU
Table II-5: Mutagenicity of the EBDCs
Table II-6: Structural Activity
Table II-7a: Summary of Average Residue Estimates for Maneb
Table II-7b: Summary of Average Residue Estimates for Mancozeb
Table II-7c: Summary of Average Residue Estimates for Metiram
Table II-8: Summary of EBDC and ETU Processing Data
Table II-9: FDA Monitoring Data and State Data for EBDCs and ETU 1985-1989
Table II-10a: Anticipated Residues for Maneb and Maneb-Derived ETU for Acute Exposure
Table II-10b: Anticipated Residues for Mancozeb and Mancozeb-Derived ETU for Acute Exposure
Table II-10c: Anticipated Residues for Metiram and Metiram-Derived ETU for Acute Exposure
Table II-11: Mixer/Loader/Applicator ETU Exposure Estimates for Sweet Corn, Grapes and Apples
Table II-12: Use Practices Information: EBDCs on Sweet Corn
Table II-13: Use Practices Information: EBDCs on Grapes
Table II-14: Commercial Nursery Ornamental EBDC Exposure Estimates
Table II-15: Homeowner EBDC Exposure Estimates
Table II-16: ETU Dietary Carcinogenic Risks
Table II-17: EBDC Individual Crop Risks (ETU Dietary Carcinogenic)
Table II-18: Developmental Dietary Risks
Table II-19: Mixer/Loader/Applicator Carcinogenic Risk Estimates (incorporating protective clothing)
Table II-20: Mixer/Loader/Applicator Developmental and Thyroid MOSs/MOEs
Table III-1: Percent of Crop Treated with EBDC Fungicides
Table III-2: Summary of Usage and Benefits of EBDCs for Selected Sites
Table III-3: Alternative Fungicides Registered for Use Against Various Potato Diseases
Table III-4: Fungicides Registered for Control of Tomato Diseases
Table III-5: Fungicides Registered for Control of Certain Apple Diseases
Table III-6: Summary of EBDC Fungicides Registered to Control Diseases of Grapes
Table IV-1: Toxicity and Status of Alternatives to the EBDCs
Table IV-2: Estimated Risks and Benefits of Crops Which Would Be Proposed for Cancellation and Retention

Table IV-3: Cost-Effectiveness Estimates for EBDC Cancellation
Table IV-4: Estimated Risks and Benefits of EBDC Crops Which Would Be Proposed for Cancellation Under the 55 Crop Approach
Table IV-5: Estimated Risks and Benefits of EBDC Crops Which Would Be Proposed for Retention Under the 55 Crop Approach
Table IV-6: Summary of M/L/A MOSs/MOEs for Developmental and Thyroid Effects and/or Carcinogenic Risks and Benefits for Sites Proposed for Cancellation

GLOSSARY

ADI: Acceptable Daily Intake: See definition of Reference Dose.

ai: Active Ingredient.

Agricultural uses:

Includes food and non-food (i.e., commercial ornamental and turf) EBDC product uses.

Data Call-In Notice:

[FIFRA Section 3(c)(2)(B)] The Agency's authority to require additional data to support existing registrations.

Efficiency Impacts:

The loss to the overall economy of the dollar value of the goods and services no longer available as a result of the cancellation action. This measure reflects the gains and losses to growers, distributers, retailers and consumers. Embedded in the efficiency measure is the producer impact; therefore, producer and efficiency impacts are not additive.

EPA: The U.S. Environmental Protection Agency; also "the Agency."

FIFRA: The Federal Insecticide, Fungicide, and Rodenticide Act (as amended 1988).

Industrial uses:

Limited to EBDC products used in industrial settings.

Invalid: Studies which have been found to be deficient in some vital parameter or those studies which have been judged not to be scientifically sound or those studies whose reliability is seriously questioned.

LC_{50}: Median Lethal Concentration: a statistically derived concentration of a substance that causes death in 50 percent of test animals, expressed as weight or volume of test substance per volume of air (e.g., mg/L or ppm).

LD_{50}: Median Lethal Dose: a statistically derived dose that causes death in 50 percent of animals when administered by the route indicated, expressed as weight of substance per unit weight of test animal (e.g., mg/kg).

LEL: Lowest Effect Level:

MOS/MOE: Margin-of-Safety/Margin-of-Exposure:

The calculation of a margin of safety or margin of exposure involves division of an appropriate NOEL by a worker's estimated exposure. The result is a unitless figure which gives an indication of how close a worker's exposure dose is in relation to the NOEL for laboratory animals.

MPI: Maximum Permissible Intake (MPI): A term relative to human dietary exposure. The MPI is expressed im mg/kg and is calculated by multiplying the RfD by the body weight of a human.

MRID: Master Record Indentification (number): EPA's system of tracking studies used in support of registrations.

NO(A)EL: No Observable (Adverse) Effect Level: A maximum dose used in a test which produces no observed (adverse) effects.

OPP: The Office of Pesticide Programs of the U.S. EPA.

ppm: Parts per million.

PADI: Provisional Acceptable Daily Intake: An acceptable daily intake of pesticide residue based on a limited toxicological data base.

PAI: Pure active ingredient.

Producer Impacts:

Affects to growers or users due to increased costs from using more expensive alternatives and losses due to possibly reduced yields.

RfD: Reference Dose: The Reference Dose (RfD) is an estimate (with uncertainty up to an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is a benchmark dose from which to gauge the potential effects of the chemical at other doses. Usually, doses less than the RfD are not likely to be associated with adverse health risks, and are therefore less likely to be of regulatory concern.

Technical:	Active ingredient as manufactured.
Technical Registrant:	Registrant of the technical material.
TMRC:	Theoretical Maximum Residue Contribution: An estimate of dietary exposure obtained by multiplying residue tolerance levels for a given pesticide by the average daily per capita food consumption figure, then adding the exposure figures for each crop. TMRC is usually expressed in terms of mg ai/kg bodyweight/day.

I. INTRODUCTION

The Environmental Protection Agency is examining the ethylene bisdithiocarbamates (maneb, mancozeb, metiram, nabam and zineb) because of carcinogenic, developmental and thyroid effects caused by ethylenethiourea (ETU), a common contaminant, metabolite and degradation product of these pesticides as outlined in the Position Document 1 (PD 1), published in 1987 (52 FR 27172). In 1986, all registrants of amobam (another EBDC pesticide) voluntarily cancelled their registrations in response to a Data Call-In Notice requiring the submission of additional data to support their product registrations.

Data available at this time has led the Agency to conclude that the continued registration of EBDC products for use on certain food crops, commercial ornamentals and home garden sites and in some industrial uses would result in unreasonable adverse effects to humans.

In determining which uses to cancel, the Agency considered the aggregate risks posed by the EBDCs and ETU, the extent to which registered uses are being supported by registrants and, where appropriate, the risks and benefits of individual uses.

A. REGULATORY BACKGROUND

1. The Special Review Process

The term "Special Review" is the name now used for the process previously called the Rebuttable Presumption Against Registration (40 CFR Part 154).

The Special Review process provides a mechanism through which the Agency gathers risk and benefit information about pesticides that appear to pose risks of adverse effects to human health or the environment that may be unreasonable. Through issuance of various notices and Technical Support Documents, the Agency publicly sets forth its position and invites participation in the Agency's review of suspect pesticides by pesticide registrants, the U.S. Department of Interior, the U.S. Department of Agriculture, user groups, environmental groups, and other interested persons.

Risk information submitted to and/or gathered by the Agency must be evaluated and considered in light of benefit information. If the Agency determines that the risks appear to outweigh the benefits, the Agency can initiate action under FIFRA to cancel, suspend, and/or require modification of the terms and conditions of registration.

2. Special Review Actions

The Federal Insecticide, Fungicide, and Rodenticide Act, as amended, (FIFRA) and its regulations require the Agency to review the risks and benefits of the uses of pesticides.

The regulatory history of the EBDCs includes a full Special Review. In 1977, The Agency initiated a Rebuttable Presumption Against Registration or RPAR (now known as a Special Review) based on the assumption that the EBDCs and ETU posed three potential risks to humans and/or the environment: carcinogenicity, developmental toxicity and acute toxicity to aquatic organisms. Three additional areas of concern were identified as thyroid toxicity, mutagenicity and skin sensitization. In 1982, the Agency concluded this Special Review by issuing a Final Determination PD 4 which adopted risk reduction measures to preclude unreasonable adverse effects pending development of additional data needed to arrive at a more refined assessment of the risks. The Agency concluded that the potential risk of acute toxicity to aquatic organisms could be reduced through the addition of a label statement warning users of a hazard to fish. Potential risks to applicators from developmental and thyroid effects could be adequately reduced by requiring protective clothing. Potential dietary exposure resulting from consumption of EBDC-treated home grown produce was addressed by a label statement highlighting preharvest intervals on labels of home use products. The Agency also concluded that there were insufficient exposure data to reach any regulatory conclusions regarding the potential risk of carcinogenic effects to humans. Additional data were required to be submitted to address mutagenic effects. The skin sensitization effect was determined not to meet the criteria for an RPAR.

On July 17, 1987, the Agency issued a second Notice of Initiation of Special Review of the ethylene bisdithiocarbamate (EBDC) pesticides (maneb, mancozeb, metiram, nabam and zineb) because of carcinogenic, developmental and thyroid effects caused by ethylenethiourea (ETU), a common contaminant, metabolite and degradation product of these pesticides. This document, also referred to as a Position Document 1 or PD 1, detailed the bases for the Agency's decision to initiate the Special Review (52 FR

27172). The Agency had determined that registrations containing the EBDC pesticides met or exceeded the 40 CFR risk criteria relating to carcinogenicity to humans from dietary exposure and a risk to applicators and mixer/loaders for thyroid and developmental effects. Subsequently, the risk criteria in 40 CFR 162.11 were superseded by new criteria set forth in 40 CFR 154.7 (a)(2) and (a)(6) relating to carcinogenicity to humans from dietary exposure and a risk to applicators and mixer/loaders for thyroid and developmental effects. Data available at that time led the Agency to conclude that the continued registration of EBDC products for use on certain food crops, on commercial ornamentals, on home garden sites and in some industrial uses might result in unreasonable adverse effects to humans. The Notice invited comments from the registrants as well as from the public. The comment period lasted 45 days and all rebuttal comments received during the comment period were evaluated.

In March 1989, Rohm and Haas (the sole registrant holding nabam agricultural uses) requested that all nabam food uses be voluntarily cancelled. The Agency's acceptance of this request is imminent. Registrants holding nabam registrations on industrial sites requested voluntary cancellation of sugar beet and sugarcane transport and flume water nabam uses in 1987, but have retained the use of nabam in sugar mill grinding, crusher or diffuser systems.

In 1986, the zineb technical registrants cancelled their registrations. At that time, the Agency notified end use suppliers of their lack of a registered supplier. After the first notification in 1986, one end use formulator agreed to support a number of uses. In July, 1989 that formulator notified the Agency that he wanted to voluntarily cancel his registrations and the Agency issued a second notice to the remaining formulators in October 1989. At this time no formulator had yet agreed to support zineb registrations.

On September 6, 1989, the four technical product registrants of maneb, mancozeb and metiram (Rohm and Haas, duPont de Nemours, Pennwalt, and BASF) applied to the Agency to amend their registrations and end use labels to remove 42 of 55 food uses and to restrict formulation of their technical products only into products labeled for uses which have been retained. Only thirteen crops were proposed for retention by the registrants. These registrants will label all their EBDC technical and end use materials manufactured after September 6, 1989; and all existing EBDC technical stocks and end use products remaining after January 2, 1990, to specify for use on only the food commodities as follows: maneb (almonds, bananas, potatoes, sugar beets and sweet corn), mancozeb (asparagus, bananas, cranberries, figs, grapes, onions, peanuts, potatoes, sugar beets, sweet corn, tomatoes and wheat), and metiram (potatoes). The affect of relabeling the technical product is that it now will become unlawful for downstream formulators to use these sources of technical in end use products labeled for use on these 42 deleted commodities. The manufacturers have also petitioned the Agency to reduce tolerances for the remaining 13 food uses. They also notified the Agency that they would not object if the Agency proposed to revoke tolerances for the 42 food uses being deleted. This voluntary action by registrants was taken in an effort to reduce possible dietary risks associated with consumption of EBDC-treated commodities. Once the registrants' action becomes final, the deleted uses cannot be reinstated until such time as the registrants apply to reinstate these uses and the Agency determines risks associated with these uses are acceptable.

Once the zineb registrations are formally cancelled and the 42 food uses are formally removed from the technical registrants' maneb, mancozeb and metiram labels, the Agency will notify the respective formulators that there is no longer a registered source of supply for these uses. No use of zineb is likely to be supported. If the maneb, mancozeb and metiram formulators want to retain any or all of the 42 uses, they must both locate an alternate source for the technical product and fulfill all data requirements for that technical product and the particular end uses retained, including those which are presently the subject of FIFRA section 3(c)(2)(B). Failure to take these steps will result in suspension under FIFRA section 3(c)(2)(B).

Until the Agency contacts the formulators, determines whether any of them will continue to support any or all of the 42 maneb, mancozeb and metiram uses which the technical registrants are dropping, and takes any suspension or cancellation actions that may be necessary, all 55 uses are still legally registered and must be considered in this Preliminary Determination. However, recognizing that all currently registered technical producers have deleted the 42 uses from their labels, and have placed language on their technical products which prohibits formulation for use on any of the removed uses, the Agency acknowledges that these 42 uses may in the near future no longer by supported by any registrant. Thus, while 55 maneb, mancozeb and metiram food crop sites are registered now, in the near term it is possible that only 13 may remain.

B. Organization of this Position Document.

This Position Document 2/3 (PD 2/3) addresses the risks and benefits of the uses of the EBDC pesticides, regulatory options, and the proposed decision. This document contains five parts. Chapter 1 is the Introduction. Chapter II discusses the potential risks of EBDC pesticide use. It includes descriptions and evaluations of the risk information, exposure data, rebuttal submissions and analyses, and the Agency's risk conclusions. Chapter III discusses the benefits of different EBDC pesticide uses, discusses the assumptions and limitations of these estimates, describes rebuttal submissions on the benefits of EBDCs and the Agency's response to these submissions. Chapter IV describes the possible regulatory options to reduce the risks and evaluates the risks and benefits of these regulatory options. Chapter V summarizes the regulatory actions which the Agency proposes to take. Chapter VI gives the references cited in this document.

C. CHEMICAL BACKGROUND

1. Chemical and Physical Characteristics

The Ethylene Bisdithiocarbamates (EBDCs) are the group of fungicides consisting of five registered pesticide active ingredients: mancozeb, maneb, metiram, nabam and zineb. Table I-1 gives the common and chemical names accepted for use in the ingredient statement on pesticide products as required by FIFRA, as well as trade names and the Chemical Abstract Service (CAS) name. Table I-2 presents the chemical structure, molecular formula and weight, solubility and other physical and chemical properties associated with each EBDC.

The chemistry of the EBDCs is complicated by their instability and their propensity to form polymers, especially in the presence of certain ubiquitous metallic ions. They begin to degrade with production and continue to degrade with storage and application. Important factors influencing chemical degradation are presence of oxygen, humidity, temperature and pH. A number of common degradation products have been reported. While all of these can result from the degradation of any EBDC, the relative proportions of the degradates appear to be different for the individual EBDCs. Ethylenethiourea (ETU) appears to be the dominant degradation product of all EBDCs and the one of greatest toxicological concern.

Table I-1

EBDC Nomenclature

Common Name	Label Name	Trade Name(s)	CAS Name
1. Mancozeb	[1]	Dithane M-45 Manzate 200	[[1,2-ethanediylbis[carbamodithioato]](2-)[manganese mixture with [[1,2-ethanediylbis[carbamatethioato], (2-)] zinc
2. Maneb	Manganese EBDC	Manzate Dithane M-22	[[1,2-ethanediylbis[carbamodithioato]](2-)] manganese
3. Metiram	[2]	Polyram	Metiram
4. Nabam	Disodium EBDC	Parzate Dithane D-14 Chem Bam Nabasan	Disodium 1,2-ethanediylbis [carbamodithioate]
5. Zineb	Zinc EBDC	Dithane Z-78	[[1,2-ethanediylbis[carbamodithioate]](2-)]zinc

---

[1] Zinc ion and manganese ethylene bisdithiocarbamate 80 percent, a coordination product of manganese 16 percent, zinc 2 percent and ethylene bisdithiocarbamate 62 percent.

[2] Mixture of 5.2 parts by weight (83.9 percent) of ammoniates of [ethylene bisdithiocarbamato]zinc with 1 part by weight (16.1 percent) ethylenebis[dithiocarbamic acid], bimolecular and trimolecular cyclic anhydrosulfides and disulfides.

Table I-2

Chemical and Physical Properties of EBDCs

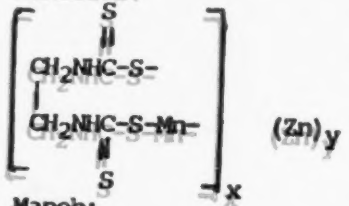
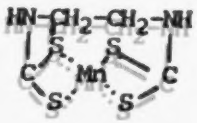
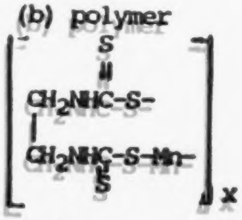
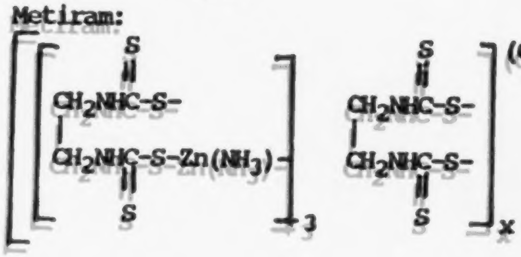
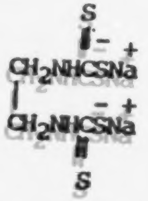
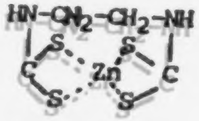
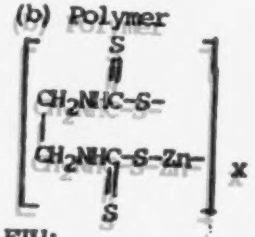
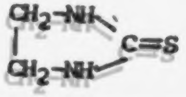
Chemical Structure	Empirical Formula	Formula Wt	Physical Properties	Solubility
Mancozeb: 	1/	271 2/	Grayish yellow powder which decomposes before melting; flash point 138° C.	Practically insoluble in water and other organic solvents.
Maneb: (a) monomer 	$C_4H_4N_2S_4Mn$	265.3	Yellow crystalline solid which decomposes before melting and on exposure to moisture or to acids.	Slightly soluble in water and insoluble in most organic solvents.
(b) polymer 	$(C_4H_4MnN_2S_4)_x$	3/	Light-colored solid which decomposes by melting and on exposure to moisture or acids.	Similar to monomer. before
Metiram: 	$(C_{16}H_{33}N_{11}S_{16}Zn_3)_x$	1088.6 2/	Light-yellow solid which decomposes at 140 C; unstable under strongly acid or alkaline conditions or a combination of heat and moisture.	Practically insoluble in water and in most organic solvents; soluble with decomposition in pyridine.

Table I-2

Chemical and Physical Properties of EBDCs (continued)

Chemical Structure	Molecular Formula	Molecular Wgt	Physical Properties	Solubility
Nabam:				
	$C_4H_6N_2Na_2S_4$	256	Colorless crystals of limited solubility; generally marketed in solution.	Soluble in water (20 pct) to form yellow solution.
Zineb: (a) Monomer				
	$C_4H_6N_2S_4Zn$	275.8	Off-white solid which decomposes before melting; negligible vapor pressure at 25°C; somewhat unstable to light, heat and moisture.	Practically insoluble in water (10p/m at 25°C) but soluble in pyridine, chloroform and carbon disulfide.
(b) Polymer				
	$(C_4H_6N_2S_4Zn)_x$	[3]	Light-colored powder produced when from concentrated aqueous solutions of nabam with zinc sulfate.	Similar to monomer.
ETU:				
	$C_3H_6N_2S$	102.2	White crystals melting at 203° to 204°C	Soluble in water; insoluble in acetone, ether, chloroform and benzene

1. Variable
2. Formula weights for mancozeb and metiram are estimated for the monomer
3. Indefinite

2. Registered Uses and Production

Approximately 225 [1] pesticide products containing EBDCs as active ingredients are federally registered. The technical materials are produced by Pennwalt Corporation (maneb); BASF (metiram); Rohm and Haas Company and E.I. duPont de Nemours (mancozeb); and Alco Chemical Corporation, Vinings Chemical Corporation and Rohm and Haas Company (nabam).

The first use of this class of chemicals as fungicides was in 1935, when nabam was used for the control of fungal diseases on tomatoes. In 1943, zinc sulfate was added to nabam suspensions to improve the fungicidal activity, and then the reaction product (zineb) became widely used to control fungal diseases on plants. The manganese salt (maneb) was developed in 1950. Since 1950, the zinc manganese complex of ethylene bisdithiocarbamates (mancozeb), the diammonium salt (amobam) and zinc ammoniates (metiram) have been developed as fungicides. In 1986, all amobam registrants voluntarily cancelled their registrations in response to receiving a requirement to submit additional data to support their product registrations.

These pesticides are intended for use as protectants against fungal pathogens and are used on a wide variety of commercial and home garden fruit, vegetable and ornamental crops and turf, as seed piece treatment, as a soil treatment and industrially as a antimicrobial in water cooling systems (towers and airwashers), oil well drilling rigs and in pulp, paper and sugar mills. Maneb [2] is primarily used for control of early and late blight diseases of potatoes and tomatoes and for control of scab and other fungal diseases of apples. Mancozeb [2] is registered on 28 food crops, the major ones being apples, grapes, potatoes, sweet corn, tomatoes and onions. Metiram [2], primarily used on potatoes for control of early and late blight, is registered for use on 12 food crops and three non-food crops. Nabam registrations for use on agricultural non-food crops (ornamentals) are currently suspended; the registrations for use on agricultural food uses have been requested to be voluntarily cancelled. Active nabam registrations are for use as biocides at industrial sites. Table I-3 lists all registered uses of the EBDCs.

---

[1] This does not include amobam, zineb, or nabam agricultural food use registrations which are all suspended and/or cancelled.

The pesticide products containing EBDCs are most commonly formulated as wettable powders, dusts and concentrates (solution and suspension). There are also other formulations available as water dispersible granules.

Approximately 12 to 18 million pounds of EBDCs have been used in the United States annually. The largest agricultural crop uses in pounds of active ingredient per year (lbs a.i./yr) are: potatoes (approximately 3.5 million lbs a.i./year), apples (approximately 3.5 million lbs a.i./year), cucurbits (approximately 2.0 million lbs a.i./year), tomatoes (approximately 1.4 million lbs a.i./year), onions (approximately

---

[2] See earlier discussion of request to amend labels for registered EBDC technical materials.

Table I-3

EBDC Registered Sites

	EBDC FUNGICIDE [a]			
SITE	MANCOZEB	MANEB	METIRAM	NABAM
Food Crops				
Almond		R		
Apple	R	R	R	
Apricot		R		
Asparagus	R	R	R	
Banana	R	R		
Barley	R			
Beans (green & dried)		R		
Broccoli		R		
Brussels Sprouts		R		
Cabbage		R		
Cantaloupe	R	R	R	
Carrot	R	R		
Casaba melon	R	R		
Cauliflower		R		
Celery	R	R	R	
Chinese Cabbage		R		
Collards		R		
Corn, Field	R			
Corn, Pop	R			
Corn, Sweet	R	R	R	
Crabapple/Quince	R			
Cranberry	R	R		
Crenshaw melon		R	R	
Cucumber	R	R	R	
Eggplant		R		
Endive		R		
Fennel	R			
Fig		R		
Grapes	R	R		
Honeydew melon		R	R	
Kale		R		
Kohlrabi		R		
Lettuce		R		
Lima beans		R		

---

a = All agricultural nabam uses have been suspended for several years and the registrant has requested voluntary cancellation of all agricultural food uses. The registrant for the technical zineb material has requested voluntary cancellation of all uses.

R = Registered use

S = Suspended use

Table I-3

EBDC Registered Sites (continued)

SITE	MANCOZEB	MANEB	METIRAM	NABAM
Food Crops				
Mustard Greens		R		
Nectarine				
Oats	R			
Onion	R	R		
Papaya	R	R		
Peach		R		
Peanuts	R		R	
Pear	R			
Pecan			R	
Peppers		R		
Pineapple propagation stock	R			
Potatoes	R	R	R	
Potatoes (seed piece)	R	R	R	
Pumpkin		R		
Rhubarb		R		
Rye	R			
Spinach		R		
Squash *	R	R		
Sugar Beets	R	R	R	
Tomato	R	R	R	
Turnips		R		
Watermelon	R	R		
Wheat	R			
Non-Food Crops				
African Violets	R			
Anthurium	R			
Arborvitae	R			
Arizona Cypress	R			
Asters	R	R		
Azalea	R	R		S
Begonia	R			
Buckeye	R			
Buffaloberry	R	R		
Camellia	R	R		S
Caprifig	R			
Carnation	R	R		S
Chrysanthemum	R	R		S
Cordyline	R			
Cotton	R		R	

---

* Mancozeb is registered only for use on summer squash

Table I-3

EBDC Registered Sites (continued)

SITE	MANCOZEB	MANEB	METIRAM	NABAM
Non-Food Crops				
Cyclamen				
Dahlias	R	R		
Delphinium				
Dieffenbachia	R			
Douglas-Fir	R			
Dracaena	R	R		
Eastern Redcedar	R			
Elm	R			
Epcot Display Crops	R	R		
Euonymous	R			
Fatsia	R			
Ficus	R			
Firethorn	R			
Flowering Crabapple	R	R		
Flowering Dogwood	R	R		
Fuchsia	R			
Geranium	R	R		
Gladiolus	R	R		S
Hawthorn	R			
Holly	R			
Hollyhock	R			
Honeysuckle	R			
Horsechestnut	R			
Hydrangea	R	R		
Iris	R	R		
Japanese Aralia	R			
Japanese Aucuba	R			
Juniper	R			
Ligustrum	R			
Lilies	R	R		
Magnolia	R			
Maple	R			
Marigold	R			
Mountain ash	R			
Mountain-laurel	R			
Narcissus	R			
Oak	R			
Orchids (Dendrobium spp.)	R			
Ornamental Conifers	R	R		
Ornamental Ferns	R			
Ornamental Flowering Plants	R	R		
Ornamental Herbaceous Plants	R			
Ornamental Plants		R		

Table I-3

EBDC Registered Sites (continued)

SITE	MANCOZEB	MANEB	METIRAM	NABAM
Non-Food Crops				
Ornamental and/or Shade Trees	R	R		
Ornamental Turf	R	R		
Ornamental Woody Shrubs/Vines	R			
Pachysandra	R			
Pansies	R	R		
Peonies	R	R		
Peperomia	R			
Philodendron	R			
Photinia	R			
Pleomele	R			
Poinsettia	R			
Pyracantha	R			
Rhododendron	R			
Rose	R	R	R	
Schefflera	R			
Skunkbush Sumac	R	R		
Snapdragon	R	R		S
Statice	R			
Syngonium	R			
Tobacco	R	R	R	
Tulips	R			
Venus Fly Trap	R			
Viburnum	R			
Walnut	R			
White Ash	R			
Zinnia	R	R		
Seed Treatment				
Barley	R	R		
Beans		R		
Corn (field)	R	R		
Cotton	R	R		
Flax	R	R		
Oats	R	R		
Peanuts	R	R		
Peas		R		
Rice	R			
Rye	R	R		
Safflower	R			
Sorghum	R	R		
Soybeans		R		
Sugar beets		R		

Table I-3

EBDC Registered Sites (continued)

SITE	MANCOZEB	MANEB	METIRAM	NABAM
Seed Treatments				
Sunflower		R		
Tomato	R			
Wheat	R	R		
Industrial Sites				
Air Washer Water System				R
Brewery Pasteurizers				R
Commercial and Industrial Water Cooling Towers				R
Fuel Oil (No. 2 oil, Intermediate fuel oil, and No. 6 oil), Lubricating Oil, and Hydraulic Fluid (storage)				R
Leather				R
Leather Processing Liquors				R
Metalworking Cutting Fluids				R
Oil Recovery Drilling Fluids				R
Oil Recovery Water				R
Preservation in Pulp and Paper Mills				R
Preservation of Adhesives and Animal Glues, Inks, Latex, Mineral Slurries, Paints and Coatings and Paper Coatings				R
Pulp and Paper Mill Systems				R
Seawater Heat Exchangers				R
Sugar Beet Flume Water Transporting and Washing Systems				R
Sugar Beet Processing Water				R
Sugarcane Processing				R

810,000 lbs a.i./year), sweet corn (approximately 700,00 lbs a.i./year) and small grains (approximately 650,000 lbs a.i./year).

3. Tolerances

The Agency has established tolerances for maneb, mancozeb, metiram and zineb. EPA has not established any tolerances for nabam residues. However, FDA has established a food additive regulation for nabam residue in beet and cane sugar and sugar molasses. These nabam residues result from the use of nabam as an industrial biocide in sugar mills. The tolerances for each of the EBDCs are expressed as zineb because available analytical methodology cannot distinguish among the various EBDCs. The tolerance levels range from 0.1 ppm to 65 ppm with most tolerances being 4-7 ppm. The tolerances for each are listed below.

The tolerances for MANEB (40 CFR 180.110) in or on these raw agricultural commodities for preharvest uses or for a combination of preharvest and postharvest uses are as follows:

(1) 45 ppm - sugar beet tops;

(2) 10 ppm - apricots, beans (succulent forms), broccoli, Brussels sprouts, cabbage, cauliflower, Chinese cabbage, collards, endive (escarole), kale, kohlrabi, lettuce, mustard greens, nectarines, papayas, peaches, rhubarb, spinach, turnip tops;

(3) 7 ppm - apples, beans (dry form), carrots, cranberries, eggplants, figs, grapes, onions, peppers, pumpkins, turnip roots;

(4) 5 ppm - celery, sweet corn;

(5) 4 ppm - bananas, cucumbers, melons, summer squash, tomatoes, winter squash;

(6) 2 ppm - apples;

(7) 0.1 ppm - almonds, potatoes.

The tolerances for METIRAM (40 CFR 180.217) are as follows:

(1) 5 ppm - celery;

(2) 4 ppm - cantaloupes, cucumbers, tomatoes;

(3) 2 ppm - apples;

(4) 0.5 ppm - pecans, potatoes.

The tolerances for MANCOZEB (40 CFR 180.176) are as follows:

(1) 65 ppm - peanut vine hay, sugar beet tops;

(2) 25 ppm - the straws of barley, oats, rye and wheat;

(3) 10 ppm - crabapples, fennel, pears, quinces, papayas;

(4) 7 ppm - apples, cranberries, grapes;

(5) 5 ppm - celery, corn fodder and forage, the grains of barley, oats, rye and wheat;

(6) 4 ppm - bananas, cucumbers, melons, summer squash, tomatoes;

(7) 2 ppm - carrots, sugar beets

(8) 0.5 ppm - popcorn grain, fresh corn, cottonseed, kidney, liver, onions, peanuts;

(9) 0.1 ppm - asparagus, corn grain;

Food and feed additive tolerances have been established for mancozeb under Section 409 of FIFRA. These tolerances are as follows:

Food Additive (40 CFR 186.6300, formerly 21 CFR 193.460)

28 ppm - raisins

20 ppm - bran of wheat, barley, oats and rye

1 ppm - flour of wheat, barley, oats and rye

Feed Additive (40 CFR 186.6300 formerly 21 CFR 561.410.

20 ppm - milled feeds of wheat, barley, oats and rye.

The tolerances for ZINEB (40 CFR 180.115) are as follows:

(1) 60 ppm - hops;

(2) 25 ppm - beet tops, Chinese cabbage, collards, romaine, Swiss chard;

(3) 10 ppm - endive, kale, lettuce, mustard greens, spinach;

(4) 7 ppm - apricots, beans, beets (garden roots only), blackberries, boysenberries, broccoli, Brussels sprouts, cabbage, carrots, cauliflower, cherries, citrus fruits, cranberries, currants, dewberries, eggplants, gooseberries, grapes, guavas, kohlrabi, loganberries, mushrooms, nectarines, onions, parsley, peaches, peanuts, pears, peas, peppers, plums (fresh prunes), pumpkins, quinces, radishes (with or without tops) or radish tops, raspberries, rutabagas (with or without tops) or rutabaga tops, salsify, strawberries, summer squash, turnips (with or without tops) or turnip greens, youngberries;

Food and feed additive tolerances have been established for mancozeb under Section 409 of FIFRA. These tolerances are as follows:

Food Additive (40 CFR 186.6300, formerly 21 CFR 193.460)

28 ppm - raisins

20 ppm - bran of wheat, barley, oats and rye

1 ppm - flour of wheat, barley, oats and rye

Feed Additive (40 CFR 186.6300 formerly 21 CFR 561.410.

20 ppm - milled feeds of wheat, barley, oats and rye.

The tolerances for ZINEB (40 CFR 180.115) are as follows:

(1) 60 ppm - hops;

(2) 25 ppm - beet tops, Chinese cabbage, collards, romaine, Swiss chard;

(3) 10 ppm - endive, kale, lettuce, mustard greens, spinach;

(4) 7 ppm - apricots, beans, beets (garden roots only), blackberries, boysenberries, broccoli, Brussels sprouts, cabbage, carrots, cauliflower, cherries, citrus fruits, cranberries, currants, dewberries, eggplants, gooseberries, grapes, guavas, kohlrabi, loganberries, mushrooms, nectarines, onions, parsley, peaches, peanuts, pears, peas, peppers, plums (fresh prunes), pumpkins, quinces, radishes (with or without tops) or radish tops, raspberries, rutabagas (with or without tops) or rutabaga tops, salsify, strawberries, summer squash, turnips (with or without tops) or turnip greens, youngberries;

(5) 5 ppm - celery, sweet corn;

(6) 4 ppm - cucumbers, melons, squash, tomatoes;

(7) 2 ppm - apples;

(8) 1 ppm - wheat;

(9) 0.1 ppm - corn grain.

The tolerances for nabam (21 CFR 173.320) established by FDA are as follows:

3 ppm - sugar beets or sugar cane from the use of nabam in sugar mill grinding, crusher or diffuser systems (secondary direct food additive).

No food additive regulation was established for the sugar beet transport and flume water use because the Agency believes that residues resulting from this use would be adequately covered by the tolerance of 3 ppm in 21 CFR 173.320. FDA also established an indirect food additive regulation covering the use of nabam as a slimicide added to the process water for the production of paper and paperboard which will contact food (21 CFR 176.300).

II. ASSESSMENT OF RISKS AND ANALYSIS OF REBUTTAL COMMENTS

A. EFFECTS OF CONCERN

1. Carcinogenicity

The carcinogenicity risk assessment process consists of four steps. In the first step, hazard identification, all relevant toxicity information is presented and a qualitative weight-of-the-evidence judgment is reached on the likelihood that the pesticide is a human carcinogen. In the second step, dose-response assessment, experimental data are used in conjunction with certain assumptions and a mathematical model to extrapolate the likely upper-bound of excess human cancer risk to the low dose range. The third step is exposure assessment in which human exposures via various routes and sources are estimated. Finally, in the fourth step, risk characterization, the results of the exposure and dose-response assessments are coupled to project the plausible upper-bound of the excess cancer risk under different conditions of exposures. This step also includes a summary of the strength of the qualitative evidence, plus a treatment of the uncertainties in the final assessment. In this chapter, the carcinogenic hazard identification and dose-response assessment will first be discussed. Then will follow a discussion of the developmental toxicity and thyroid effect concerns. After a discussion of dietary and non-dietary exposure, risk estimates for all three effects will be presented, followed by a rebuttal analysis.

a. Hazard Identification

Despite its comprehensive data base on ETU, the Agency currently does not have adequate carcinogenicity studies for any of the EBDC parent compounds. Earlier this year, the Agency received preliminary results of a rat carcinogenicity study on mancozeb which is due in June, 1991. The registrants conducting the mancozeb studies have indicated that the final results should be available well before this deadline, probably in time to be included in the PD 4. Depending on the results of this study, adjustments to the potency factor (Q*) may be necessary. Carcinogenicity studies with both the rat and mouse have been required under FIFRA section 3(c)(2)(B) for each of the EBDC chemicals through either Registration Standards or Data Call-In Notices. Data from these studies may not be available for the scheduled PD 4. If any of these studies indicate there are additional unacceptable risks, the Agency will take further regulatory action.

The Agency does have an extensive data base on the carcinogenicity of ETU. Most recently, ETU was tested for carcinogenicity in rats and mice by the National Testing Program (NTP) using both an *in utero* protocol and the standard NTP protocol. The NTP pathology peer review group met in late August, 1988. The data tables from the review of these studies were received by the Agency in March, 1989; the final report is expected to be issued in late 1989 or early 1990. The data from the portion of the studies conducted in accordance with the standard protocol for a carcinogenicity study have been used in the current risk assessment to determine the new preliminary Q_1*. The remaining data (namely those also encompassing in utero exposures) will be reviewed over the next several months, and included in the final risk assessment, as appropriate. In any case, the ETU Q* is not likely to change significantly from that derived originally (less than an order of magnitude).

In the first EBDC PD 1 (1977) the original presumption of carcinogenicity was based on five studies that reported positive carcinogenic responses when either maneb, zineb or ETU was tested on laboratory animals. Metiram was tested for carcinogenicity in rats (Hunter et al., 1981) and mice (Hunter et al., 1979); however, results of these studies are considered inconclusive due to faulty study design. Carcinogenicity studies are not yet available on mancozeb and nabam although a preliminary report on mancozeb has been submitted to the Agency under FIFRA section 6(a)(2).

The five positive carcinogenic studies on maneb, zineb and ETU are summarized as follows. Balin (1970) observed increased numbers of lung adenomas in mice fed weekly doses of maneb (500 mg/kg/body weight) by stomach tube for 6 weeks. Likewise, Chernov et. al. (1969) observed increased occurrence of lung adenomas in mice fed weekly doses of zineb (3500 mg/kg/body weight) by stomach tube for 6 weeks. When weekly doses of zineb were reduced to 1750 mg/kg/body weight but continued for 11 weeks, lung adenomas were again observed in treated animals but not in control groups. Innes et. al. (1969) observed marked increases in liver tumors in mice fed single daily doses of ETU (646 ppm) for over 80 weeks. Ulland et. al. (1972) fed two different doses of ETU (350 or 175 ppm) daily to rats for 18 months. Thyroid carcinomas developed in test animals at both dose levels but did not develop in controls. Graham et. al. (1975) fed ETU to rats at doses of 500, 250, 25 or 5 ppm for nearly 2 years. A dose-related increase in thyroid follicular cell carcinomas and adenocarcinomas was observed at 500 and 250 ppm; thyroid follicular cell adenomas at 250 ppm; and thyroid follicular cell hyperplasia at 250, 125, 25 and 5 ppm.

Although in 1982 the Agency concluded that qualitatively the EBDCs may have the potential to cause carcinogenic effects in humans, it agreed with rebutters that several deficiencies in the Balin and Chernov et. al. studies made them unreliable for use in a quantitative risk assessment. At that time, the Agency decided that there were insufficient data to reach any regulatory conclusions concerning potential carcinogenic effects to humans. However, the uncertainties did not pertain to whether ETU induced tumors in animals. In relation to the ETU studies (Innes et. al., Ulland et. al., and Graham et. al.), the Agency believed then and continues to believe that results of these studies constituted sufficient evidence to show that ETU is carcinogenic.

In 1982 the Agency relied on the Innes chronic mouse study on ETU to conduct a quantitative risk assessment and stated in its 1982 EBDC Decision Document (PD 4) that ETU is a strong animal carcinogen and has the potential to cause cancer in humans.

The same three ETU studies, along with portions of the new NTP studies were used by the Agency in its current carcinogenic risk assessment. A more detailed discussion of each follows:

1) Innes et. al. (1969)

In this study, two hybrid strains of mice were used, (C57BL/6 x C3H/Anf)F1 and (C57BL/6 x AKR)F1. Eighteen mice per sex per group were used in the treatment group. Only one dose was tested which was stated to be the maximum tolerated dose. When the mice were seven days old, 215 mg/kg ETU was given by gavage. At 28 days of age, the mice were started on diets containing 646 ppm (96.9 mg/kg/day) of ETU. After a total of 83 weeks of treatment, the mice were sacrificed. Histopathology consisted of examination of all major organs and of all grossly visible lesions. Thyroid glands were not examined. The incidence of liver tumors seen which were not classified as adenomas or carcinomas but only as hepatomas is outlined in the following table which was taken from EPA's Cancer Assessment Group (CAG) risk assessment document on ethylene bisdithiocarbamates (CAG, June 7, 1979). The Agency concluded that, although information on the type and incidence of hepatomas would have been helpful in their deliberations, the high incidence (56-100%) in the ETU-treated animals compared to the controls (0-21%) was certainly indicative of an carcinogenic response to the chemical. See Hauswirth, June 16, 1988.

Table II-1

Liver Tumors in ETU-Treated Mice

STRAIN	DOSE (ppm)	MALES	FEMALES
(C57BL/6 x C3H/Anf)F1	0	3/14 (21%)	0/18 (0%)
(C57BL/6 x C3H/Anf)F1	646*	14/16 (88%)	18/18 (100%)
(C57BL/6 x AKR)F1	0	1/18 (6%)	0/18 (0%)
(C57BL/6 x AKR)F1	646*	18/18 (100%)	9/16 (56%)

---

* after 28 days

2) Ulland et. al. (1972)

In a study reported by Ulland, groups of 26 Charles River rats per sex were administered 175 or 350 ppm (8.75 and 17.5 mg/kg/day respectively) of ETU in the diet for 18 months. The control group consisted of 32 male and 32 female rats. After 18 months of treatment, 5 rats/sex were sacrificed and the remaining rats were placed on control diets until termination of the study at 24 months. No thyroid lesions were seen in the control group. The number of animals examined was not given. All five male rats in the high dose group sacrificed at 18 months had hyperplastic goiter; 3 had thyroid follicular cell cancer. The authors did state that "possibly additional carcinomas could have been discovered if serial sections had been done in the goitrous gland." The following table (Table II-2) was taken from the published report and lists the incidence of thyroid lesions in ETU-treated rats.

Table II-2

Tumor Induction in Rats by ETU

	Dose and No. Affected			
	350 ppm		175ppm	
Lesion	males	females	males	females
Thyroid carcinoma** (follicular)	17	8	3	3
Thyroid solid cell adenoma	0	1	0	2
Hyperplastic goiter	17	13	9	6
Simple goiter	2	4	4	2
Liver hyperplastic nodule	1	0	2	1

** Two with lung metastases

3) Graham et. al. (1975)

In this study, five groups of 5 week old male and female Charles River rats were placed on diets containing 0, 5, 25, 125, 250 or 500 ppm (0, 0.05, 0.25, 6.25, 12.5, 25 mg/kg/day) ETU. The duration of the study was 2 years. At 18 and 24 months, 5 rats per sex from each group were given 5 uCi ^{131}I (microcuries of radioactive iodine) by i.p. injection, fasted for 24 hours and sacrificed. At the end of 66 weeks, 3 rats/sex/group were placed on the control diet for the remainder of the study to determine the reversibility of thyroid toxicity due to ETU. Only rats with enlarged thyroids were placed in these groups. Ten animals/sex/group were also sacrificed at 2, 6 and 12 months. Data on these animals were not included in this report.

Body weight gain was statistically significantly reduced ($p<0.01$) at the highest dose tested at 18 and 24 months for both males and females as compared to controls: males (-18 percent) and females (-15 percent) at 18 months; males (-26 percent) and females (-27 percent) at 24 months. Increased ^{131}I uptake was statistically significantly increased in male rats at 18 months in the 25 and 125 ppm groups and decreased at 500 ppm. At 24 months in male rats, ^{131}I uptake was significantly increased in the 5 ppm group and decreased in the 500 ppm group. Because of ^{131}I uptake variability, there were no statistically significant differences in ^{131}I uptake in female rats.

Histopathology incidence data were combined for males and females. An increase in the number of rats with cataracts/ keratitis and with thyroid follicular adenocarcinoma/carcinoma was observed in the groups fed 250 and 500 ppm (12.5, 25 mg/kg/day) ETU; with thyroid adenomas in the 250 ppm (12.5 mg/kg/day) group; and with thyroid hyperplasia in the 5, 25, 125 and 250 ppm (0.25, mg/kg/day) groups. The LEL is 5 ppm (0.25 mg/kg/day) for the effects of ETU on the thyroid in this study. Relevant data are summarized in Table II-3.

Table II-3

Histopathology Data from Graham et al. (1975)

PARAMETER	TUMOR INCIDENCE DATA FOR RATS GIVEN ETU (ppm)					
	0	5	25	125	250	500
Pathological lesions						
Cataracts/keratitis	2	1	0	2	6	12
Thyroid carcinoma/ adenocarcinoma (follicular)	2	2	1	2	16	62
Thyroid adenomas	2	–	5	1	21	3
Thyroid hyperplasia	4	20	41	44	27	3
Parathyroid hyperplasia	6	11	8	2	3	0

Statistics were not reported for the histopathological data. Historical control data were not available. An attempt was made to obtain more detailed information (i.e. incidence data for males and females, separately) on this study from FDA; however, the final report of this study has not yet been located in their files.

In August 1986, the Toxicology Branch Peer Review Committee (composed of scientists within the Office of Pesticide Programs as well as other Agency programs) met to evaluate and to discuss the adequacy of the above-mentioned three ETU carcinogenicity studies. Other ancillary information was also considered in the determination of ETU's carcinogenicity (i.e., mutagenicity data, structure activity relationships, etc.). The Committee agreed that each of the three studies, when considered separately, did not meet current test standards for the evaluation of carcinogenicity. However, the Committee believed that, collectively, along with the other information considered, they were adequate to conclude that ETU is carcinogenic in rats and mice. Subsequent to the Peer Review (1987), the slides from the Innes mouse study (referred to above as the third study) were reread by Anver of ICF-Clement using the NTP diagnosis criteria. In rereading the slides of the B6C3F$_1$ strain, Anver classified 72 percent of the original hepatomas as carcinomas in both males and females. In 1969 when the study was conducted, the general term "hepatomas" was used to collectively describe both benign and malignant liver tumors. Additionally, 83 percent of the hepatomas in the males (15/18) of the second strain tested were classified as carcinomas while 13 percent of the hepatomas in the females were classified as carcinomas. The incidence of liver tumors in both sexes of both strains in control groups was either non-existent or greatly diminished compared to the magnitude of the response in the treated groups.

4) National Toxicology Program (NTP) (1989)

The National Toxicology Program (NTP) recently made data available on ETU in studies conducted in rats and mice. These studies were of an unusually complex design when compared with the usual NTP carcinogenicity bioassay. Besides including treatment groups which received the traditional pattern of exposure (beginning at about eight weeks of age and continuing until the end of the experiment at two years), there also were treatment groups in which animals were exposed in utero essentially from the moment of conception, continuing throughout their lifetimes. While preliminary evaluation of data from these additional exposure scenarios indicate tumor responses somewhat different from those seen in the standard treatment groups, only data from the standard treatment group have been used in this current risk assessment since the remaining data are still under review. It is anticipated that all of the data from this complex exposure paradigm will be evaluated thoroughly in the next few months. This evaluation will be incorporated into the final risk assessment which will accompany the final regulatory decision on the EBDCs.

As mentioned above, data from the studies of traditional design (standard treatment group) were used in this current risk assessment. Before conducting the long term mouse study, a 90-day feeding study was conducted to determine appropriate dose levels. Ten mice per sex per dose received either 0, 125, 250, 500, 1000 or 2000 ppm of ETU. The most important effects observed were the histopathologic changes in the thyroid and liver. Follicular cell hyperplasia of the thyroid follicles was present in most of the male and female mice receiving 1000 and 2000 ppm ETU. Altered strain affinity of hepatocytes in the centrilobular areas in the liver (central portion of the liver lobe) was primarily present in male and female mice in the higher dose groups. This lesion was however, more severe in male mice. Cellular atypia and/or alteration of hepatocytes in the centrilobular areas in the liver was also observed in ten of ten male mice at 2000 ppm. No females had this lesion in the 2000 ppm group. However, one of ten females in each of the 250 and 1000 ppm dose groups showed this lesion.

Based on the results of the 90-day mouse feeding study, animals were fed doses of 0, 333 or 1000 ppm ETU in the diet for up to two years. The results were as follows: In the female mice, treated at the low dose, 30% of the animals exhibited liver adenomas only while an additional 58% showed liver carcinomas for a combined total of 88%. At the high dose, only 2% exhibited adenomas while 96% were diagnosed with carcinomas. This contrasts sharply with a total of only 8% of the females in the control group exhibiting either adenomas (4%) or carcinomas (4%). Males also showed dose-related effects in the liver. Although the incidences of liver adenomas (16%) and carcinomas (30%) (total of 47% of animals with tumors) was obviously higher in male than female controls, the treated males showed significantly higher tumor rates when compared against their concurrent controls. Virtually all males exhibited tumors at the high dose (2% with adenomas, 98% of them with carcinomas) while a total of 68% of the males at the low dose had tumors (adenomas = 28%;

carcinomas = 40%). Centrilobular cytomegaly (scattered giant cells in the area of the central portion of the liver lobe which are generally recognized as potential precursors to carcinogenicity) was evident in both treated groups of both sexes but not observed in the controls. Cellular necrosis was not observed in any group. The thyroid gland in female mice showed dose related increases in follicular cell hyperplasia when compared to controls (4%, 26%, 94%). Male mice showed follicular cell hyperplasia only at the high dose tested (0%, 0%, 88%). Female mice showed statistically significant increases in follicular cell multiple adenomas and carcinomas at the high dose only. No thyroid carcinomas or adenomas were observed in controls. In males, follicular cell adenomas and carcinomas appeared to a greater extent in the high dose group total (62%) than in controls (2%) or the low dose group (2%).

Before conducting the long term rat studies, a 90-day feeding study was conducted to determine appropriate dose levels. Ten rats per sex per dose received 0, 60, 125, 250, 500 and 750 ppm ETU. Based upon the parameters examined, it was concluded that the most important effects observed were those histopathologic changes in the thyroid. Follicular hyperplasia and thyroid adenomas were seen in both male and female rats primarily in the 250 ppm and higher dose groups. These lesions were more severe and involved a larger number of males in all dose groups.

In the new NTP study conducted on rats, the thyroid gland was the principal target organ for ETU. Based on the 90-day rat feeding study, animals were fed ETU in their diet at levels of 0, 83 or 250 ppm for up to two years. Hyperplasia ranged between 0-9% for control groups, whereas hyperplasia in all treated groups was between 18 and 64%. Follicular cell adenocarcinomas occurred in 58% of the high dose group of males compared to 2% in controls. In females, it was 16% for adenocarcinomas at the high dose compared with 4% for controls. (Rinde, August 10, 1989, Preliminary Peer Review of Ethylene Thiourea).

b. Mutagenicity

ETU and the EBDCs have been tested for mutagenicity in several assay systems. Results of the available studies were both positive and negative. However, the body of evidence for ETU and the individual EBDCs suggest that they are capable of inducing a variety of genotoxic effects (Dearfield, September 25, 1989 and July 22, 1988). These include responses in gene mutation assays, structural chromosomal assays, and other genotoxic effects. The assay systems and results are summarized in Tables II-4 and Table II-5 below.

A major consideration that should be taken into account when examining the genotoxicity of ETU is the magnitude of these positive responses. While ETU induces a variety of genotoxic endpoints, it does not appear to be a potent genotoxic agent. Since ETU does not appear to be very potent, and is not extremely

Table II-4

Mutagenicity of ETU

ASSAY SYSTEM	RESULT
Transformation in C3H 10T 1/2 cells	Negative
Transformation for promotion in C3H 10T 1/2 cells	Negative
Drosophila, sex-linked recessive lethal	Negative
E. Coli WP_2 Reversion	Negative
Chromosomal aberrations in Chinese Hamster DON cells	Negative
Mouse dominant lethal	Negative
Chromosomal aberrations in bone marrow - mice	Positive
UDS - HeLa cells	Positive
UDS - human fibroblasts	Negative
Micronucleus test - mice	Negative
B. Subtilis Rec assay	Positive
Transformation in BHK 21 cells	Positive
Sister chromatid exchange in bone marrow and liver cells (in vivo)	Negative
Sister chromatid exchange in CHO cells (in vitro)	Negative
Chromosomal aberrations in CHO cells	Negative
Gene mutation - mouse lymphoma cells	Negative
Gene mutation - CHO-HGPRT assay	Negative
S. cerevisiae - mitotic recombinants	Positive
Ames Assay his G-46, TA 98, 100, 1535,1537,1538	Positive, negative

Table II-5

Mutagenicity of the EBDCs
(Acceptable Studies Submitted to the Agency)

TEST SYSTEM	METIRAM	MANEB	MANCOZEB	NABAM
Ames Salmonella	NT	negative	negative	NT
Sister chromatid exchange-CHO cells	positive	negative	positive	positive
Host mediated assay - mice	negative	negative	negative	equivocal
Cytogenetics - rats bone marrow	negative	negative	negative	negative
Unscheduled DNA synthesis - rat	negative	negative	negative	positive
Gene mutation - CHO cells	positive	negative	negative	positive
Transformation C3H 10T 1/2	negative	negative	negative	negative
Transformation promotion assay C3H 10T 11/2	equivocal	NT	negative	NT
Saccharomyces cerevisiae D3 mitotic recombin.	positive	positive	positive	NT

NT = not tested

toxic to test cells and organisms, it is not surprising to find reviewed that ETU does not induce effects in many of the assays. Therefore, in many instances, positive and negative results in the same assay are reported from different investigators, but these results may be dependent upon the test conditions in each individual laboratory. Usually there are problems with many of the negative assays in protocol or reporting and in many studies the concentration levels are not high enough for an adequate test.

An additional concern for ETU may be the aspect of nitrosation of ETU. There are suggestions that ureas (such as ethylenethioureas) can be nitrosated with sodium nitrite at appropriate acidities. Many ethylene bisdithiocarbamate-treated products are cooked and eaten. With ETU as a metabolite along with a contaminant as a nitrosating source, humans could be exposed to conditions where nitrosation in the stomach may occur. Nitrosated ETU and ETU in combination with sodium nitrite have been demonstrated to induce potent genotoxic effects in gene mutation assays and in _in vivo_ micronucleus and chromosomal aberration assays. Therefore, this aspect of ETU genotoxicity should be a concern if humans are exposed to ETU above certain amounts.

In many instances, the induced genotoxic effects by the EBDCs are not particularly striking, for example, in the SCE assays. However, in some instances, the response is significantly large, e.g. the response to mancozeb in the in vitro cytogenetic assays. Also, there is no single assay where all the EBDCs provide consistently elevated and substantial positive responses. This demonstrates that these compounds apparently are not consistent in their genetic activity with many negative results found in addition to the positive results. An in depth examination is necessary to ascertain their potential genotoxicity. Of the five EBDCs tested, mancozeb induced a larger number of positive effects (Deerfield, 1989), including positive cytogenetic results from exposed humans (Jablonicka et al, 1989) that would provide the most evidence among the EBDCs for a mutagenicity concern. (It should be noted that mancozeb had more test results available than the other EBDCs.) Overall, therefore, it appears that the EBDCs do present a genotoxicity concern with each of the individual compounds inducing enough of a variety of genetic effects to elicit such a concern. This evidence provides some support in a weight-of-evidence consideration for potential carcinogenicity of these compounds.

It is well recognized that a correlation exists between genotoxic agents and carcinogenicity in that many, but not all, mutagenic agents contribute to or induce tumor formation. Experimental evidence has shown that ETU is capable of altering DNA in a variety of test systems. ETU has been shown to produce thyroid tumors in the rat and liver and thyroid tumors in the mouse. It can, therefore, be said that the positive mutagenicity findings provide general support for the carcinogenic observations of ETU in both rats and mice. However, if it can be shown that the positive results in these mutagenicity studies have no direct relevance to the initiation of thyroid tumors in the rat, one might argue that the thyroid tumors in the rat may be the result of a positive physiological feedback mechanism resulting from the inhibition of thyroid hormone production. If only thyroid tumors were observed following exposure to these substances, valid evidence supporting a hormonally based mechanism of activity might lead the Agency to modify the way it views the carcinogenic potential of ethylenethiourea and introduce the concept of threshold into the quantification of carcinogenic risk. However, these chemicals also induce liver tumors and no supportable or adequate scientific argument has been put forth to persuade the Agency to alter its current policy for the quantitative assessment of this endpoint.

c. Non-Genotoxic Tumor Formation (Threshold Concept)

The physiological relationship between the pituitary gland and thyroid gland is well known. Decreased levels of thyroid hormones which threaten homeostasis results in the enhanced secretion of thyroid stimulating hormone (TSH) from the anterior pituitary with a subsequent rise in thyroid hormone levels. The return of thyroid hormone levels to acceptable levels results in a negative feedback mechanism with decreased levels of thyroid stimulating hormone being secreted by the anterior pituitary and a subsequent decrease in the production of thyroid hormone. An imbalance in this relationship where decreased thyroid hormone levels cannot be compensated for results in the chronic stimulation of the thyroid with attendant changes in thyroid gland morphology (follicular cell neoplasia). This positive feed-back mechanism is well documented and can be induced experimentally by a variety of proven means. Thyroid gland follicular cell neoplasia has been experimentally induced by low iodine diets, subtotal thyroidectomy, intrasplenic transplants of thyroid tissue and transplantation of anterior pituitary tumors producing thyroid stimulating hormone. Ethylene thiourea (ETU) has been demonstrated to inhibit iodide peroxidase _in vitro_ and may have the same effect on the thyroid gland _in vivo_. Iodide peroxidase catalyzes the iodination of tyrosine and the coupling of the resultant iodotyrosyl residues to produce the active thyroid hormones. Thus, ETU interferes with the biosynthesis of thyroid hormones by inhibiting iodide peroxidase with the resultant effect of positive feedback to the pituitary for as long as is sufficient to maintain decreased thyroid hormone levels. In animal experiments, ETU induces thyroid tumors under test conditions of chronic administration and adequate dosing. The argument can therefore be advanced that at dose levels of ETU that do not interfere with iodide peroxidase or interfere with it at some non-critical level, ETU should not cause thyroid tumors since the dose of ETU will be at a level below which an exacerbated positive feedback would not occur. This argument has been presented to the Agency's FIFRA Scientific Advisory Panel and the Science Advisory Board. Each has given its cautious approval to this approach. Although the approach has been sanctioned, the threshold concept itself is still being considered by the Agency and will be presented to the FIFRA Scientific Advisory Panel in 1990.

d. Summary of ETU Metabolic and Pharmacokinetic Properties

Animal metabolism of the EBDCs is rapid and ETU and ethylene isdiisothiocyanate sulfide (EBIS) are major metabolites. Carbon disulfide and dimethylamine are formed in rats treated orally with mancozeb, maneb and zineb (Lyman 1971; Seidler et al. 1970; Vonk 1974; Truhaut 1973). Formation of these metabolites is expected following ingestion of EBDCs due to the acid environment of the stomach. Truhaut et al. (1973) identified EBIS, ETU, EU (ethyleneurea) and EDA (ethylenediamine) in the feces and urine of rats treated with mancozeb. After a single oral dose of ^{14}C mancozeb in rats, about 15 percent of the total radioactivity was found in the urine and about 71 percent (47 percent as unchanged mancozeb) appeared in the feces (Lyman, 1971). Before elimination, radioactivity localized in the thyroid gland. Measurements indicated that roughly 18 mole percent of the EBDCs were converted to ETU. Within 5 days after a single oral dose of radiolabeled maneb was administered to rats, about 55 percent of the total radioactivity was found in the urine and feces (Seidler et al. 1970). Metabolites of zineb were identified as EDA, ETU, and EBIS. ETU and EBIS were the major metabolites found in urine of rats treated with zineb (Truhaut, 1973).

Jordan and Neal (1979) studied the metabolism of ^{14}C maneb and zineb administered orally (0.25 m. mole/kg) in mice. After 48 hours, 91 percent of the maneb and 65 percent of the zineb were recovered. Of total recovered radioactivity, less than 10 percent was found in the urine after administration of each chemical. Of metabolites recovered in the urine, about 15 percent was ETU with most of the balance as unidentified polar products. No EBIS was found. In the same experiment, ETU and EBIS were fed separately to mice. One hundred percent of the administered radioactivity from the ETU (0.25 m. mole/kg) was recovered rapidly with almost 50 percent found in the urine. Of that, 52 percent was unchanged ETU, 12 percent was EU with 37 percent polar products. After 48 hours, only 54 percent of the administered radioactivity from ^{14}C -EBIS (0.25 m. mole/kg) was recovered. Of this, 74 percent was in the urine, mostly as polar products, but with some conversion to ETU. The authors concluded that a small percentage of orally administered maneb and zineb is converted to ETU in mice. The ETU is further metabolized in part, followed by excretion in the urine and, perhaps, the feces.

In a comparative study, Iverson et al. (1980) examined the metabolism of ETU in rats and cats. In rats, urinary excretion of radioactivity after 24 hours was 82 percent of the total dose administered. Besides, ETU (62.6 percent of recovered radioactivity), imidazoline, inidazoline, EU and other metabolites were found. In contrast, in cats, S-methyl ETU represented 64.3 percent of urinary radioactivity, with the balance as ETU, EU and other metabolites.

Studies of the metabolism of ETU administered to pregnant animals have revealed that mice and rats differ in the disposition of the chemical, and that mice are able to metabolize ETU more completely and more rapidly than rats (Battelle, 1982). The calculated half-life of ETU and its metabolites in maternal blood was 5.5 ± 0.4 and 9.4 ± 0.6 hours for mice and rats, respectively (Ruddick et al., 1977). Except for the thyroid, there is virtually no accumulation of ETU in treated rats, since over 80 percent of the absorbed dose is eliminated in the urine 24 hours after dosing (Kato et al., 1976). This is in contrast to an accumulation in mouse liver and a 40 percent urinary excretion over the same time span (Battelle, 1982).

In summary, although the above studies indicate general metabolic pathways for the EBDCs and ETU in laboratory animals, recovery of radioactivity was generally incomplete and the balance of metabolites present was not adequately identified. The studies show that ETU may be formed by diverse pathways from the parent compounds and may be further metabolized giving rise to several byproducts, not all of which are characterized.

e. Structure-Activity-Relationship

The common EBDC degradate and metabolite ETU is structurally related to the EBDCs and several thyroid inhibitors. EBDC and ETU structures are shown in Table II-6.

Chronic studies on thiourea have shown that it induces hepatomas and thyroid enlargement in rats. Thyroid neoplasia was not observed. In another study in rats, thiourea was reported to induce malignant tumors of the face. Thiourea was negative for mutagenicity in the Ames Salmonella assay for tester strains TA1530 and 1538 but positive in TA100, negative for sex-linked recessive lethals in Drosophila and for unscheduled DNA synthesis in rat hepatocytes, positive for mutagenicity in S. cerevisiae D6, and positive for transformation in Syrian hamster embryo cells and Rauscher MLV/RE cells.

Methimazole, propylthiouracil and thiouracil all induce thyroid tumors in rats. Propylthiouracil also induces thyroid tumors in hamsters and guinea pigs and pituitary adenomas in mice. Thiouracil induces hepatomas and thyroid tumors in mice.

f. Human Studies

The Agency is not aware of any valid human epidemiology studies which evaluated exposure to ETU or any of the EBDCs.

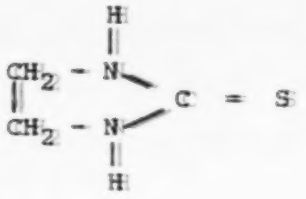
g. Weight-of-Evidence for Carcinogenicity

The Agency considers the following facts regarding the toxicology data on ETU to be important in the weight-of-evidence determination of the carcinogenic potential of ETU.

Table II-6

Structural Activity

ETU



Thyroid Inhibitors

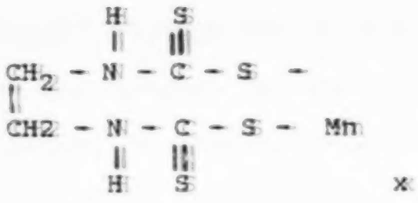
Propylthiouracil

Thiourea

Methimazole

Thiouracil

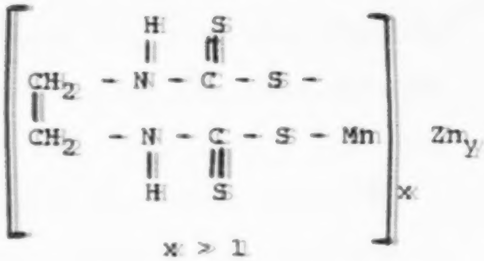
Maneb



$$\left[\begin{array}{l} CH_2-\overset{H}{N}-\overset{S}{\overset{\|}{C}}-S- \\ \| \\ CH2-\underset{H}{N}-\underset{S}{\underset{\|}{C}}-S-Mn \end{array}\right]_x$$

x > 1

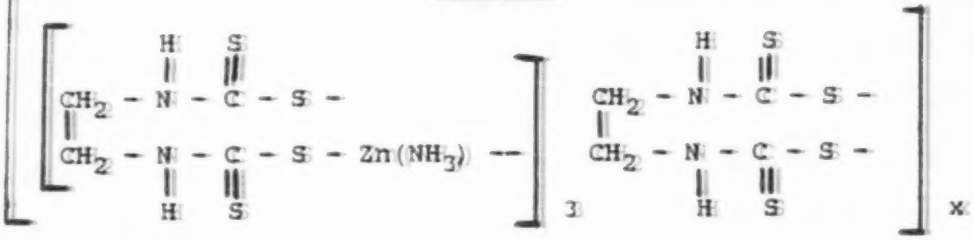
Mancozeb



$$\left[\begin{array}{l} CH_2-\overset{H}{N}-\overset{S}{\overset{\|}{C}}-S- \\ \| \\ CH_2-\underset{H}{N}-\underset{S}{\underset{\|}{C}}-S-Mn \end{array}\right]_x Zn_y$$

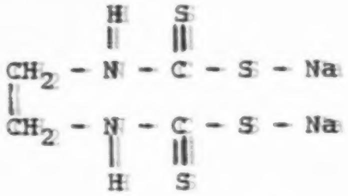
x > 1

Metiram



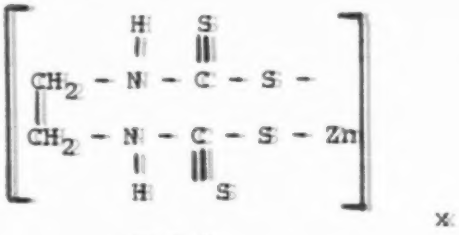
$$\left[\left[\begin{array}{l} CH_2-\overset{H}{N}-\overset{S}{\overset{\|}{C}}-S- \\ \| \\ CH_2-\underset{H}{N}-\underset{S}{\underset{\|}{C}}-S-Zn(NH_3)- \end{array}\right]_3 \begin{array}{l} CH_2-\overset{H}{N}-\overset{S}{\overset{\|}{C}}-S- \\ \| \\ CH_2-\underset{H}{N}-\underset{S}{\underset{\|}{C}}-S- \end{array}\right]_x$$

Nabam



$$\begin{array}{l} CH_2-\overset{H}{N}-\overset{S}{\overset{\|}{C}}-S-Na \\ \| \\ CH_2-\underset{H}{N}-\underset{S}{\underset{\|}{C}}-S-Na \end{array}$$

Zineb



$$\left[\begin{array}{l} CH_2-\overset{H}{N}-\overset{S}{\overset{\|}{C}}-S- \\ \| \\ CH_2-\underset{H}{N}-\underset{S}{\underset{\|}{C}}-S-Zn \end{array}\right]_x$$

x > 1

- ETU has been shown to induce thyroid adenomas and carcinomas (mostly follicular) in F344 and Charles River CD rats. ETU has been shown to induce hepatomas in (C57BL/6 x C3H/Anf) F1 and (C56BL/6 x AKR)F1 mice after 83 weeks of treatment (Innes, 1969) and adenomas/carcinomas in the livers of B6C3F$_1$ mice, along with thyroid and pituitary adenomas and thyroid carcinomas (NTP, 1982).
- ETU has been shown to induce liver tumors (single and multiple adenomas and carcinomas) in mice and thyroid effects (hyperplasia and follicular cell adenomas and carcinomas) in mice and rats. Pituitary adenomas were also increased in female mice.
- ETU has shown both positive and negative results in a variety of mutagenicity studies. There was enough of a mutagenicity concern to provide supportive evidence of the carcinogenic effect. Nabam, metiram and mancozeb have been shown to be positive for sister chromatid exchanges in CHO cells and nabam and mancozeb for unscheduled DNA synthesis in rat hepatocytes; maneb, mancozeb and nabam are negative in the Ames Salmonella assay; and metiram and nabam are positive for gene mutation in CHO cells.
- ETU is structurally related to, and a degradate and metabolite of, the EBDCs. Qualitatively, maneb and zineb have been shown to cause carcinogenic effects (lung adenomas) in mice (Balin, 1970 and Chernov et al., 1969). However, the results of these studies were considered inconclusive due to faulty study design and

considered unreliable for use in a quantitative risk assessment. The Agency now has preliminary information (in addition to the NTP/ETU study) submitted under FIFRA section 6(a)(2) on mancozeb. Evaluation of thyroid tissues from Sprague-Dawley rats indicates that, at the high dose tested, (0, 20, 60, 125 or 750 ppm) there is a statistically significant increase in follicular cell adenomas and carcinomas in male rats and a statistically significant increase in females when follicular cell adenomas and carcinomas are combined. The incidence of follicular cell lesions in all other groups appear comparable to control values.

- ETU is also structurally similar to thiourea, methimazole, propylthiouracil and thiouracil. Thiourea and thiouracil induce hepatomas in rats and mice, respectively. Methimazole, propylthiouracil and thiouracil all induce thyroid tumors in rats. Propylthiouracil also induces pituitary adenomas in mice.
- ETU is rapidly metabolized in both the rat and the Rhesus monkey. Excretion is primarily in the urine.

h. Dose Response

The Agency concludes, based upon the available evidence, that ETU **meets** the criteria of a Group B_2 Carcinogen (probable human carcinogen) according to its Guidelines for Carcinogen Risk Assessment. This classification is based on the following:

- ETU induced an increased incidence of thyroid follicular cell adenomas and adenocarcinomas in F344 and Charles River CD rats (three separate studies) and of liver tumors in three strains of mice [(C57BL/6 x C3H/Anf) F1, (C57BL/6 x AKR)F1, and B6C3F$_1$]. ETU induced thyroid tumors in rats after one year or less of treatment. It also induced a high incidence of both thyroid tumors in rats and hepatomas in mice to an unusual degree in a single experiment.

This classification is also supported by positive structure-activity data since several other thyroid inhibitors (i.e., thiouracil and thiourea) have been found to induce hepatomas and/or thyroid tumors in rodents. The Agency also notes that in the rat studies, evidence of progression of the neoplastic process in the thyroid was present. Results of the available mutagenicity studies were both positive and negative. There was enough of a mutagenicity concern to provide supportive evidence of the carcinogenic effect.

While the Agency agrees that, while not all of the carcinogenicity studies considered were carried out in strict accordance with current Guideline for Carcinogen Risk Assessment studies, it considers the studies adequate to conclude that ETU is carcinogenic to rats and mice due to the nature and magnitude of the dose-response seen.

i. Determination of Carcinogen Potency Factor (Q_1*) for Risk Calculations

The original Q_1* for ETU was derived by the Agency's Cancer Assessment Group (CAG) from the Innes mouse study. It was calculated to be 0.14 (mg/kg/day)$^{-1}$. At that time, it was chosen over other possible outcomes because it gave the highest Q_1*.

The new preliminary Q_1* [0.6 (mg/kg/day)$^{-1}$] which is being used in this document to calculate risks is based on data on female mouse liver tumors observed in a new NTP study on ETU. Although NTP data on the rat thyroid were made available to the Agency to calculate a new Q_1*, the mouse data were chosen because it provided a slightly higher potency factor.

As stated earlier, the new NTP studies included a number of unique exposure scenarios. Data associated with the _in utero_ exposure will be reviewed to determine if these data would provide a more valid basis from which to derive a quantitative estimate of hazard/risk. In that case, the preliminary Q_1* used in this current risk assessment could change in either direction depending upon the dose rate to the fetus determined during the _in utero_ phase of the animal's lifetime exposure.

2. Developmental Effects

The no-observable-adverse-effect level (NOAEL) for developmental toxicity resulting from exposure to ETU is ≤5.0 mg/kg. ETU was shown to be developmentally toxic at dose levels lower than those that produced no apparent maternal toxicity or fetal lethality. At 5.0 mg/kg/day, which was the lowest dose tested, developmental toxicity was observed in the form of delayed ossification of the parietal bone (in the skull). Although the author (Khera, 1973) indicated that this observation was limited to a few large sized litters and involved small areas, the effect was observed in offspring of dams treated prior to pregnancy through day 15 of gestation as well as in dams treated only during days 6-15 of gestation in a separate experiment. In both experiments, delayed ossification was clearly dose related and at higher rates than in controls and appears to be a sensitive indicator of exposure to ETU. It would appear, therefore, that there is no no-observable-effect level in this study. It was also stated in the publication by Khera, that in personal communication with W.H. Newsome, the ETU was detected in term fetuses at concentrations comparable to those found in maternal tissues following oral treatment with 20 or 40 mg/kg of ETU from days 7 to 20 of pregnancy and it could, therefore, not be determined whether the malformations arose as a result of direct action on the fetus or indirectly by altering maternal thyroid or other functions. In the previously-mentioned new NTP study conducted on rats and mice, results indicated that ETU affected thyroid function as manifested by thyroid hyperplasia in both species. However, a mouse study conducted by Teramoto showed no developmental toxicity at doses as high as 800 mg/kg/day by gavage (0, 200, 400, 800 ppm). Administration of T3/T4 with ETU to pregnant rats appears to reduce the incidence of some of these effects. ETU has also been shown to cause a wide variety of anomalies in rats (Ruddick et. al., 1975). It would appear that simple inhibition of the thyroid gland may not necessarily be the mechanism by which developmental effects are manifested in rats. Although a no-observable-effect level (NOEL) was not established in the Khera rat study, the Agency believes the NOAEL is close to the NOEL and could be used for the purposes of calculating Margins-of-Safety/Margins-of-Exposure.

A rabbit study conducted with nabam has recently been submitted to the Agency. The available data show nabam to be a developmental toxicant eliciting major malformations and other manifestations of developmental toxicity in a dose related manner and at all tested dose levels. The findings include hydrocephaly (confirmed after visceral examination with soft spot and/or domed cranium observed externally), frontals and parietals incompletely ossified, increased incidence of resorptions and an overall increased incidence of malformed fetuses per litter. In addition, the data did not uncover any apparent maternal toxicity at the lowest dose, 3 mg/kg/day nabam. An increased incidence of abortions and other effects were apparent at the high dose level, 60 mg/kg/day nabam. (NOTE: Animals were dosed with Aquatreat DN-30 which is 30 percent nabam. Therefore, tested dose levels were actually 0, 3, 30, and 60 mg/kg/day nabam). It was the opinion of the reviewer that, even though the study did contain some deficiencies, the rabbit study is a valid study and the results support the conclusion that nabam is a developmental toxicant in the rabbit.

3. Thyroid Effects

Two subchronic ETU toxicity studies can be found in the open literature. The purpose of both studies was to examine in some detail the subchronic effects of ETU on the thyroid. In the Graham study (1972), levels of 50, 100, 500 or 750 ppm were fed in the diets to male Osborne-Mendel rats for 30, 60, 90 and 120 days. A NOEL was not determined in this study due to significant effects of ETU seen on thyroid weights at all dosage levels at 120 days. In the Freudenthal (1977) rat study, a NOEL of 5 ppm was determined for the effects of ETU on the thyroid of Charles River Sprague-Dawley rats. Thyroid toxicity seen at levels above 5 ppm consisted of thyroid hyperplasia, decreased uptake of ^{125}I (radioactive iodine) by the thyroid and decreased serum levels of T3 and T4. The LEL (Lowest Effect Level) was 25 ppm. Similar effects were observed in the mouse and rat subchronic studies done prior to the new NTP bioassays in these studies.

In a study done by Battelle Columbus Laboratories (1982) in Sprague-Dawley rats, it was shown that serum T3 and T4 levels returned to normal within 2-4 weeks after discontinuing ETU in the diet. Administration of T3/T4 along with ETU did not completely reverse the effects of ETU on T3/T4 levels.

4. Aquatic organisms

Although not a subject of this Special Review, existing data indicate that maneb may pose acute risks to aquatic organisms. Data received by the Agency (in response to April 1987 Comprehensive Data Call-In Notices) show the following acute 96 hour LC_{50} s for rainbow trout: maneb (0.20 ppm), mancozeb (0.46 ppm), and metiram (between 46-100 ppm). Based on available cold water fish toxicity data, maneb and mancozeb are highly toxic; and metiram is slightly toxic. Maneb was similarly demonstrated to be highly toxic to warm water fish and invertebrates. The LC_{50} values for bluegill sunfish and Daphnia were 0.27 ppm and 0.31 ppm, respectively.

Additional chronic aquatic organism and environmental fate data are needed to further examine the risk of maneb to aquatic organisms. EPA has required a complete set of environmental fate data through the maneb, mancozeb, metiram and nabam Registration Standards. Once these data are received and reviewed, the Agency will make a determination concerning these potential risks.

5. Avian toxicity

Although not a subject of this Special Review, a letter from the registrants summarizing data from studies done in response to the April 1987 Mancozeb Registration Standard indicates that mancozeb may cause reproductive effects in birds. Although the Agency has not yet reviewed the studies themselves, the preliminary summary suggests adverse effects on mallard reproduction at dietary concentrations of 250 ppm and higher, and on bobwhite reproduction at 500 and 1000 ppm. The final evaluation is expected to support a NOEL of at least 250 ppm in the bobwhite. An estimate of the NOEL in the mallard based on plotting data for the most sensitive parameter (number of eggs laid vs. log of the dose) is 50 ppm. In order to confirm this NOEL, a second reproduction study is being conducted. When results of these studies are received and reviewed, the Agency will make a determination concerning these potential risks.

6. Ground water

Although not a subject of this Special Review, the Agency has requested small scale retrospective ground water monitoring data for each of the EBDC parent compounds through Data Call-In Notices dated October, 1988. These Data Call-In Notices were issued in response to environmental fate data (submitted by EBDC registrants in response to the July 20, 1984 Data Call-In Notices) which indicated that EBDC parent compounds have the potential to leach into ground water. Data have been submitted to the Agency documenting the occurrence of ETU in ground water in Maine in areas where maneb and mancozeb are the most widely used pesticides. No other incidents of EBDCs or their degradates in ground water are know (EPA/OPP, 1988). The Agency has decided that additional data are needed to define further the extent of any ground water problem. These data are due to the Agency in February 1992.

B. EXPOSURE ANALYSIS

Because of the EBDCs' broad spectrum of use on food crops, the entire U. S. population may be exposed to EBDC and ETU residues through the diet. Also, mixers/loaders/applicators may be exposed to the EBDCs and ETU primarily from dermal contact and, to a lesser degree, from inhalation of the substance applied on crop and non-crop sites, including nabam's use in cooling towers, oil rigs, and sugar and pulp and paper mills.

1. Dietary Exposure

Dietary exposure is both chronic and acute. When EBDC fungicides are used on food crops, the Agency is concerned about chronic exposure to ETU because of the carcinogenicity and thyroid effects of ETU, and acute exposure to ETU because of the developmental toxicity of ETU. Both chronic and acute exposure to ETU may occur by direct exposure by eating EBDC-treated food with ETU residues and by *in vivo* conversion of EBDC residues to ETU.

a. Background

In the PD 1, the Agency expressed concern regarding the chronic dietary exposure to consumers of food treated with EBDC pesticides. This concern was based on a assessment of dietary exposure and risk from ETU derived from mancozeb due to carcinogenic risk of ETU. This analysis was discussed in the Mancozeb Registration Standard (Guidance for the Reregistration of Pesticide Products containing Mancozeb as the Active Ingredient, EPA, April, 1987). The Agency was concerned about consumers exposed to ETU due to ETU residues in or on EBDC-treated crops as well as through in vivo conversion of the EBDC residues to ETU. At that time, the Agency estimated dietary exposure to only mancozeb and ETU from commodities treated with mancozeb, as it only had acceptable residue data on this EBDC fungicide at that time. The exposure estimates were based on average residues of mancozeb and ETU from residue data on crops treated with mancozeb. These data were adequately supported by storage stability data. The average residues of mancozeb and ETU were adjusted to take into account percent of crop treated. At the time of the PD 1, percent of crop treated data were available for EBDCs as a group, but not for each individual EBDC fungicide. Consequently, the percent of crop treated for the EBDCs as a group was used to estimate risk in the PD 1.

Although not discussed in the EBDC PD 1, the Agency also conducted dietary exposure assessments for the developmental and thyroid effects of ETU. These exposure analyses were discussed in the Mancozeb Registration Standard.

Prior to the publication of the PD 1, the Agency had crop residue data for maneb and metiram from the 1985 and part of the 1986 growing seasons. These data were not considered in the PD 1 because they were not supported by storage stability studies conducted concurrently with the residue studies. Storage stability studies conducted after the 1985 growing season suggested there may be significant degradation of both EBDC and ETU residues during frozen storage. The amount of data available on nabam and ETU residues derived from nabam also were too limited to use in the PD 1.

Since the PD 1, the Agency has received crop residue, processing and storage stability data for maneb and metiram (and ETU derived from maneb and metiram) as a response to the Special Review Storage Stability Data Call-In Notice of 3/31/87, and additional data received as a response to earlier Data Call-In Notices. After the comment period for the PD 1 closed, additional crop residue and processing data were received from Rohm and Haas in response to the Mancozeb Registration Standard, from Pennwalt in response to the Maneb Registration Standard, and from BASF in response to the Metiram Registration Standard. Additional processing studies on leafy greens were received from the National Food Processors Association (NFPA) and other interested groups. The Agency also has obtained updated percent of crop treated information, listed by individual EBDC chemical. (See Chapter III, Table III-1.) These data and information have been incorporated into the Agency's current Dietary Exposure Assessment. One registrant (Rohm and Haas) submitted existing market basket type monitoring data for EBDCs and ETU conducted in the late 1970s. Additional monitoring data for EBDCs and ETU also have been received from FDA and the States. These data are discussed in the Agency's Response to Comments.

The results of the limited FDA, State and registrant-submitted monitoring studies available suggest that residues of EBDC's and ETU may substantially degrade between harvest and consumption. Due to the limited number of samples tested, these data were considered too limited to use for a quantitative dietary exposure estimate in this document. Therefore, for use in further refining dietary exposure estimates, EPA has required EBDC registrants to conduct and submit a residue monitoring study. Data have been required for one major crop in each crop group for which EBDCs are registered, for major processed commodities and for meat and milk. Extrapolations will be made by crop groupings to other commodities. All data are due to EPA in September 1990. Issuance of the Agency's Final Determination PD 4 is anticipated in Spring 1991. The Agency will consider any such data received by this date. If the market basket survey is not received or produces invalid results, the Agency will make its final determination dietary risk assessment on the best available data it has at that time.

For the EBDC PD 2/3, exposure to the EBDC parent compounds and ETU have been considered. Both chronic and acute exposure analyses were performed for maneb, mancozeb, metiram, nabam and for ETU derived from each EBDC compound (See Hummel, 1988, 1989; Kovacs, 1986; and Tomerlin, 1988, 1989 analyses).

The approach to estimating the anticipated residues for chronic or acute exposure is governed by the type of data available for a given pesticide/crop combination. For the EBDCs, field trial, processing, washing and cooking data were available for maneb, mancozeb and metiram. Limited monitoring data for EBDCs and ETU were also available but the number of samples per commodity and the number of commodities analyzed were too limited to use for dietary exposure assessment. (Note that due to analytical limitations, monitoring data cannot distinguish among the various EBDCs, nor can it determine the source of any ETU present.) There are no raw agricultural commodity tolerances established for nabam. Regulations have been established by the Food and Drug Administration under 21 CFR 173.320 (b)(3) for nabam residues following application to sugar mill grinding, crusher and/or diffuser systems (secondary direct food additive); and under 21 CFR 176.300 for the use of nabam as a slimicide added to the process water for the production of paper and paperboard which will contact food (indirect food additive). These two uses are under FDA's jurisdiction.

b. Carcinogenicity and Thyroid Effects

For chronic exposure, the Agency attempts to estimate the average residue in food at the time of consumption (Anticipated Residue). The anticipated residue is then multiplied by an average lifetime food consumption estimate (based on the overall average consumption of infants to adults from the 1977-1978 USDA Nationwide Food Consumption Survey for the U. S. population and the estimated percent of crop treated) to yield the Anticipated Residue Contribution (ARC). The ARC is then multiplied by the carcinogen potency factor (Q_1*) for each parent compound to estimate the potential carcinogenic effect. The ARC is also compared to the Reference Dose (RFD) to estimate potential for non-carcinogenic effects (in this case, on the thyroid). Chronic analyses also were performed for carcinogenicity of ETU from the use of each EBDC parent compound. Tables II-7 A, B and C present residue estimates used in the chronic exposure analysis for maneb, mancozeb, metiram and nabam, respectively.

Carcinogenic risk was estimated as a combination of several factors: 1) ETU exposure both from direct exposure (in or on EBDC-treated food commodities) and from indirect exposure (resulting from metabolic conversion of EBDC residues to ETU in the body after consumption of EBDC-treated food commodities), 2) a time factor, and 3) a body surface correction factor. Assessing carcinogenic risk in this manner provides an upper bound estimate of average individual risk which applies to 240 million people.

Since food commodities treated with EBDC pesticides contain both EBDC residues and ETU residues, two exposure estimates are necessary to calculate total ETU dietary exposure. A direct ETU exposure estimate is calculated from ETU residues found in or on estimate is calculated from EBDC residue estimates on food commodities that metabolically convert to ETU in the body (also referred to as _in vivo_ conversion). To estimate indirect ETU estimated exposure, EBDC exposure is multiplied by a metabolic conversion factor of 0.075 (7.5 percent). Total ETU exposure is the sum of estimated exposure from these two sources.

Table II-7a

Summary of Average Residue Estimates for Maneb

Commodity	Average Residues (ppm) Maneb	ETU
Carrots	10	0.023
washed	7.5	0.023
cooked	6.0	1.3
Potatoes	0.013	0.002
washed	0.009	0.002
baked flesh	0.009	0.002
baked skins	0.009	0.004
whole, cooked	0.009	0.002
Sugar Beets	0.35	0.004
White Sugar	0.13	0.004
Molasses	0.13	0.004
Dried Pulp	0.46	0.004
Sugar Beet Tops	42	0.50
Turnips	14	0.29
washed	10	0.29
cooked	8.2	2.0
Turnip Tops	48	0.29
washed	14	0.12
cooked	0.48	2.2
Onions, Green	6.1	0.27
washed	4.6	0.27
Onions, bulb	5.9	0.16
washed	4.4	0.16
cooked	3.5	0.90
Celery	65	0.35
washed	19	0.15
cooked	0.65	3.0
Lettuce, Leaf;Endive	17	0.18
washed	5.0	0.076
Lettuce, Head	0.28	0.007
washed	0.084	0.003
Spinach,Collards	23.	0.34
washed	7.0	0.14
cooked	0.23	1.3
Mustard Greens	51.	0.15
washed	15	0.063
cooked	0.51	2.2
Broccoli,Kohlrabi, Brussels Sprouts	20.	0.092
washed	6.0	0.039
cooked	0.20	0.9
Cabbage, untrimmed Cauliflower, Chinese Cabbage	3.0	0.040

Table II-7a (Cont.)

Summary of Average Residue Estimates for Maneb

Commodity	Average Residues (ppm) Maneb	ETU
Cabbage, trimmed	1.0	0.003
washed	0.30	0.003
cooked	0.010	0.044
Kale	22.	0.11
washed	6.6	0.046
cooked	0.22	1.0
Beans, Succulent	3.1	0.075
Cooked/canned	0.031	0.31
Cooked/frozen	0.22	0.18
Cooked/pureed	0.031	0.23
Cannery waste	4.0	0.14
Beans, Dry	2.5	0.045
washed	0.18	0.045
cooked	0.025	0.24
Succulent Bean Vines	640	1.7
Dry Bean Vines	220	6.2
Peppers	6.4	0.03
washed	2.5	0.03
cooked	0.32	0.032
Tomatoes, Eggplant	2.6	0.002
washed	1.0	0.002
cooked	0.13	0.11
Wet pomace	1.6	0.002
Dry pomace	0.86	0.52
Canned whole	0.86	0.002
Catsup	0.86	0.002
Paste	0.86	0.52
Juice from past	0.86	0.52
Cucumber	0.90	0.075
washed	0.35	0.075
Squash	0.230	0.003
washed	0.137	0.003
cooked	0.018	0.046
Melons, Pumpkin	0.28	0.004
washed	0.11	0.004
washed, peeled	0.056	0.002
peeled, cooked	0.007	0.014
Apples	7.2	0.043
washed	4.3	0.043
cooked	0.65	0.075
fresh Juice	0.36	0.11
Cooked Juice	0.36	0.075
Wet Pomace	33	0.53
Dry Pomace	93	3.2
Apple Sauce	0.65	0.075
Apple Baby Food	0.36	0.075

Table II-7a (Cont.)

Summary of Average Residue Estimates for Maneb

Commodity	Average Residues (ppm) Maneb	ETU
Apricots	34	2.5
washed	21	2.5
cooked	3.1	2.6
Peaches	69	1.4
washed	41	1.4
cooked	6.2	1.7
Nectarines	21	0.41
washed	12	0.41
cooked	1.9	0.50
Grapes	4.0	0.014
washed	2.4	0.014
cooked	0.36	0.032
Dry Pomace	2.6	0.20
Wet Pomace	2.4	0.07
Thick juice	0.25	1.9
Raisins	1.1	0.24
Raisin Waste	6.5	0.50
Almonds	0.44	0.010
Almond Hulls	120	0.020
Sweet Corn (K+CWHR)	0.088	0.003
washed,cooked kernel	0.013	0.003
Corn Fodder	33	0.088
Corn Cannery Waste	3.8	0.048
Bananas, whole	0.070	0.016
Banana, edible portion	0.035	0.008
Figs	0.95	0.015
Cranberries	0.40	0.012
Papayas	2.8	0.002
pulp	1.4	0.002
Rhubarb-see celery		

Commodity	Average Residues (ppm) Maneb	ETU
Milk Local Milkshed	0.050	0.018
Milk National Basis	0	0
Beef Liver	0	0
Beef Kidney	0	0
Beef Muscle	0	0
Beef Fat	0	0
Eggs	0	0
Poultry Liver	0	0
Poultry Kidney	0	0
Poultry Muscle	0	0
Poultry Fat	0	0

food commodities. An indirect ETU exposure

Table II-7b

Summary of Average Residue Estimates for Mancozeb

Commodity	Average Residue (ppm) Mancozeb	 ETU
Carrots	0.090	0.002
washed	0.068	0.002
cooked	0.054	0.011
Potatoes	0.013	0.002
washed	0.009	0.002
cooked	0.009	0.003
Wet Peel	0.013	0.003
Dry Peel	0.013	0.003
Potato Chips	0.013	0.003
Potato Granules	0.013	0.003
Sugar Beets	0.21	0.002
White Sugar	0.040	0.002
Molasses	0.040	0.002
Dried Pulp	0.40	0.002
Sugar Beet Tops	39	0.35
onions, dry bulb	0.060	0.002
washed	0.045	0.002
cooked	0.036	0.008
Celery, untrimmed	1.7	0.010
trimmed	1.1	0.004
washed	0.34	0.004
cooked	0.011	0.050
Tomatoes	2.5	0.017
washed	0.98	0.017
cooked	0.13	0.098
Juice	0.12	0.052
Wet Pomace	0.088	0.040
Dry Pomace	0.35	0.12
Puree, sauce, ketchup	0.28	0.098
Paste	0.83	0.18
Cucumbers	0.55	0.010
washed	0.22	0.010
cooked	0.028	0.028
Melons	2.8	0.020
peeled	1.4	0.010
washed	0.54	0.010
cooked	0.069	0.054
Squash	0.53	0.002
washed	0.21	0.002
cooked	0.027	0.017

Table II-7b (Cont.)

Summary of Average Residue Estimates for Mancozeb

	Average Residue (ppm)	
Commodity	Mancozeb	ETU
Apples	8.3	0.29
washed	5.0	0.29
cooked	0.25	0.33
Wet pomace	12.	0.33
Dry pomace	57	0.29
Juice, canned	1.6	0.29
Canned apples (sauce, slices)	0.25	0.29
Pears	7.1	0.020
washed	4.3	0.020
cooked	0.21	0.052
Grapes	0.83	0.010
washed	0.50	0.010
cooked	0.025	0.014
Dry Pomace	0.50	0.027
Wet Pomace	0.25	0.010
Juice	0.003	0.024
Raisins	0.30	0.010
Raisin Waste	1.8	0.012
Corn, Sweet	0.16	0.003
cooked	0.16	0.003
Corn Fodder	30.	0.14
Corn, Field		
grain & proc. comm.	0.020	0.002
Field Corn Fodder	5.2	0.002
Wheat grain	0.13	0.002
bran	0.28	0.002
shorts	0.15	0.002
flour	0.15	0.002
bread	0.08	0.002
Wheat Straw	9.2	0.020
Oats, Rye - see wheat		
Barley	0.72	0.002
kernel	1.40	0.012
bran	0.04	0.018
flour	0.04	0.002
husk	5.2	0.089
rough	4.9	0.013
shorts	0.04	0.018
Barley straw	30	0.20
Asparagus	0.040	0.002
washed	0.003	0.002
cooked	0.0004	0.003
Bananas, whole	0.66	0.002
peeled	0.33	0.001
cooked	0.010	0.005

Table II-7b (Cont.)

Summary of Average Residue Estimates for Mancozeb

Commodity	Average Residue (ppm) Mancozeb	ETU
Caprifigs - no data		
Cottonseed (all commodities)	0.29	0.030
Cranberries	2.1	0.020
washed	1.3	0.020
cooked	0.063	0.029
Papayas	5.8	0.13
peeled	2.9	0.065
washed	1.7	0.065
cooked	0.087	0.078
Peanuts (all commodities)	0.020	0.002
hulls	0.13	0.002
hay	7.4	0.010
Pineapple - no data		

Commodity	Average Residues (ppm) Mancozeb	ETU
Milk Local Milkshed	0.020	0.008
Milk National Basis	0.01	0.004
Beef Liver	0.04	0.007
Beef Kidney	0.02	0.005
Beef Muscle	0.02	0.004
Beef Fat	0.002	0.002
Eggs	0.001	0.0004
Poultry Liver	0.001	0.001
Poultry Kidney	0.001	0.002
Poultry Muscle	0.001	0.002

Table II-7c

Summary of Average Residue Estimates for Metiram

	Average Residue (ppm)	
Commodity	Metiram	ETU
Potatoes	0.020	0.021
washed	0.015	0.021
baked flesh	0.015	0.021
baked skins	0.015	0.022
Wet Peel	0.020	0.021
Dry Peel	0.020	0.021
Potato Chips	0.020	0.021
Potato Granules	0.020	0.021
baked whole	0.015	0.021
Sugar Beets	0.003	0.050
White Sugar	0.001	0.050
Molasses	0.002	0.11
Dried Pulp	0.039	0.051
Celery *	65	0.35
washed	19	0.15
cooked	0.65	3.0
Tomatoes	0.53	0.030
washed	0.21	0.030
cooked	0.027	0.054
Wet pomace	0.064	0.037
Dry pomace	0.12	0.035
Canned whole	0.027	0.043
Catsup	0.032	0.090
Paste	0.042	0.11
Juice from paste	0.027	0.046
Puree	0.037	0.081
Cantaloupe *	0.28	0.004
washed and peeled	0.056	0.002
peeled and cooked	0.007	0.014
Apples	3.3	0.47
washed	2.0	0.47
cooked	0.30	0.48
Fresh Juice	0.17	0.50
Cooked Juice	0.17	0.48
Wet Pomace	15	0.69
Dry Pomace	43	1.9
Apple Sauce	0.30	0.48
Apple Baby Food	0.16	0.48
Sweet Corn (K+CWHR)*	0.088	0.003
washed, cooked	0.013	0.003
Pecans	0.020	0.002
Peanuts	0.020	0.010
Meal	0.020	0.010
Oil	0.020	0.010
Peanut Hulls	0.020	0.070
Peanut Vines	28	0.80

Table II-7c (Cont.)

Summary of Average Residue Estimates for Metiram

Commodity	Average Residue (ppm) Metiram	ETU
Milk - Local Milkshed	0.030	0.020
Milk - National Basis	0	0
Beef Liver	0	0
Beef Kidney	0	0
Beef Muscle	0	0
Beef Fat	0	0
Eggs	0	0
Poultry Liver	0	0
Poultry Kidney	0	0
Poultry Muscle	0	0
Poultry Fat	0	0

---

*Data are translated from maneb, since no recent residue data were submitted for metiram residues on celery, cantaloupe, or sweet corn.

Time is another factor to be considered when estimating carcinogenic risk. Estimates of upper-bound lifetime carcinogenic risks for adults are based on assumed exposure over a 70-year lifespan. For the overall U.S. population, exposure is assumed to continue over an entire lifetime. When estimating carcinogenic risks for children and infants, adjustments are made to estimate exposure for the time period they remain in a specific age subgroup (e.g., infants who are 0 to 1 year olds and younger children who are 1 to 6 year olds). Consideration is also taken into account for the specific types of foods typically consumed by each age subgroup.

Currently, the Agency also incorporates body surface correction factors when calculating carcinogenic risks. The carcinogen potency factor (Q_1*) for ETU is based upon studies in which animals are dosed over virtually their entire lives. Usually, EPA makes a correction of the dose comparing the ratio of body weight to surface area of the adult animal tested versus the ratio of body weight to surface area of adult humans. However, the ratios of body surface areas to body weights for children and infants are not the same as is this ratio for adults and thus an additional correction factor is included to more accurately estimate the risk to these two subgroups. The Q_1* of 0.6 $(mg/kg/day)^{-1}$ used to calculate dietary risk for the overall population was further adjusted to account for infants by 0.51 percent and for children aged 1 to 6 by 0.64 percent, based upon information described in Diem and Lentner, 1975. This additional body weight to surface area adjustment to the "adult" Q_1* to estimate carcinogenic risk to children and infants has not been done previously by the Agency for other pesticides. The Agency invites comment on this approach.

There are two basic approaches to estimating anticipated residues. The first uses field or "farm gate" data provided to the Agency as a requirement in the tolerance setting process. (See Residue Chemistry Guidelines, Subdivision O, Pesticide Assessment Guidelines.) For chronic exposure, the average residue from field trial data may be multiplied by processing and degradation factors to yield the anticipated residue estimate. Processing factors may include factors to account for commercial processing, washing,cooking or other food preparation methods. The second approach would be to base the estimate on monitoring data for raw and processed commodities. Monitoring data have the potential to reflect the effect of different application rates, PHIs, storage times and conditions and percent of crop treated. The estimate from monitoring data could be adjusted for the effect of washing, cooking or other food preparation methods.

Commercial processing may increase or decrease residue levels. For the EBDCs, processing may convert parent EBDC residues to ETU. Currently, EPA requires processing studies only if there is a possibility that the processing may concentrate residues such that total residues in the processed commodity will exceed total residue levels in the raw agricultural commodity. Processing studies where residues are expected to be reduced are optional. These include studies on washing, trimming, peeling, freezing, canning and cooking (boiling, baking and frying). Without these data, the Agency estimated dietary exposure based on field trial data.

Many of the basic food commodities (e.g., grains, potatoes and apples) are stored either under cold or ambient storage conditions for extensive periods of time. Decline of residues in stored commodities can be factored into the anticipated residue estimate, provided information on the commercial distribution of stored vs. unstored commodities is available.

Finally, whichever process for estimating residues is used, _in vivo_ conversion of EBDCs to ETU must be taken into account. Since final carcinogenicity studies for the specific EBDC's are unavailable, the Agency's exposure and risk assessment for each EBDC chemical includes the ability of the EBDC chemicals to be converted metabolically to ETU. EBDC data available to the Agency indicate that the ETU metabolic conversion rate in humans for all parent EBDC compounds is approximately 7.5 percent of the amount of EBDC consumed. The Agency has multiplied the exposure estimates for each EBDC parent compound by 7.5 percent to account for the ability of EBDCs to metabolically convert to ETU _in vivo_ on a weight for weight basis.

To estimate "farm gate" residues for maneb, metiram and mancozeb, the Agency used the average EBDC residues from residue field trial data from studies conducted close to the maximum rate, minimum PHI, and at least the typical number of applications that are allowable on the label. If residues from a lower application rate than the maximum application rate were used, then the residue estimate was increased proportionally to the maximum application rate to determine the maximum residues which might occur. For ETU residue estimates, the Agency used the average ETU residue from field trial data, corrected for the degradation of ETU in frozen sample storage when that degradation in storage in that commodity or a similar commodity exceeded 20 percent. To correct for degradation in frozen storage, the Agency divided the ETU level as determined in field studies by the fraction of ETU remaining as determined in controlled frozen storage stability studies.

Farm gate residue estimates were further refined to take into account some of the effects of treatment of the commodity after harvest, such as commercial processing, washing, peeling, trimming, and cooking. Rohm and Haas submitted a study conducted by Chilton Research Services (MRID #403819-17) in 1977 which indicated that an estimated 99 percent of restaurants, households and food processors use some type of preparation procedure for foods (washing, soaking, rinsing, peeling, trimming) except that an estimated 93 percent of restaurants use a processing procedure on apples. EBDC residue estimates were reduced by up to 93 percent when the effects of washing were taken into account. ETU residue estimates were increased by up to 12.5 percent of the EBDC residue estimate to account for the effects of cooking. Peeling and trimming factors were determined for a few commodities. The effects of cold or ambient storage used in normal channels of trade could not be factored into the analysis since no data were available for these effects.

For EBDC anticipated residue estimates in commercial processed commodities of apples, sugar beets, tomatoes, snap beans, grapes, corn, peanuts, barley and wheat the Agency multiplied the anticipated residue estimate for the raw agricultural commodity by a concentration/reduction factor determined in processing studies required to support tolerances. For potatoes, no concentration of mancozeb or metiram was observed and no conversion of EBDC to ETU was observed, since all samples had non-detectable residues. Residue estimates for potatoes and potato products were made based on limits of detection.

For ETU anticipated residue estimates in processed commodities of apples, sugar beets, tomatoes, snap beans, grapes, barley and wheat the Agency multiplied the EBDC anticipated residue estimate for the raw agricultural commodity by the percent conversion (parent EBDC to ETU) determined in processing studies, and added the ETU residue estimate from the raw agricultural commodity.

No data on the effects of ambient or cold storage used in normal channels of trade are available for any crops treated with EBDC fungicides. However, based on available data, it is known that residues of EBDCs and ETU decline during frozen storage

(Kovacs, 1987) and, therefore, would also be expected to decline in ambient and/or cold storage.

For EBDCs, washing and cooking studies (Hummel, 1988a; Hummel, 1989) have been conducted on tomatoes, spinach, potatoes and carrots. Some additional washing data were found in processing studies. Washing reduces residues of EBDC parent compound, but has little effect on ETU residue levels. Cooking converts EBDC residues to ETU residues. Washing factors for reduction of EBDC residues on washing and cooking and factors for the percent conversion of EBDC to ETU on cooking were determined from these studies. Peeling factors were available for bananas and papayas. Trimming factors were available for celery from mancozeb residue studies (Hummel, 1988c). The processing factors are summarized below in Table II-8.

Table II-8
Summary of EBDC and ETU Processing Factors

Commodity	Ave. EBDC Washing Factor	Ave. EBDC Cooking Factor	EBDC to ETU Percent Conversion
Apples (Fruit)	0.60 X	0.03 - 0.09 X	0.45%
Tomatoes (Fruiting Veg.)	0.39 X	0.05 X	1.7 - 4.6%
Leafy Vegetables	0.30 X	<0.01 X	4.1%
Beans	0.07 X	0.01 X	7.6%
Carrots (Root Crops)	0.75 X	0.60 X	12.5%
		Peeling Factors EBDC	 ETU
Bananas, Papayas		0.5 X	0.5 X

Apple EBDC residues and EBDC residues in other fruits were multiplied by a factor of 0.6 to account for the effect of washing and by a factor of 0.03 - 0.09 to account for the effect of cooking. ETU residues on apples and other fruits were adjusted by a 0.45 percent conversion factor of EBDC to ETU on cooking. This factor is the EBDC to ETU conversion factor from the metiram processing study for applesauce (Hummel, 1988b; 1989). Residues in other commodities were estimated in a similar manner. The washing and cooking factors and percent conversion from EBDC to ETU upon cooking are determined using the EBDC residue in the raw agricultural commodity, since the conversion factors were determined from cooking and processing studies using unwashed raw agricultural commodities. Residues in baked whole potatoes have been estimated by assuming that baked whole potatoes contain 10 percent baked skins and 90 percent baked flesh.

The FDA and several states (CA, FL and NY) monitor for EBDCs and/or ETU. No USDA monitoring data are available for EBDCs or ETU. The FDA, as part of their enforcement program for pesticides, collects four types of monitoring data: domestic surveillance, domestic compliance, import surveillance and import compliance. FDA, in their surveillance monitoring program, monitors a wide variety of agricultural and processed commodities for numerous contaminants, including pesticides, using multiresidue methods of analysis which are capable of determining a variety of contaminants from a single sample analysis. In their surveillance monitoring program, FDA also conducts selective surveys to acquire information on specific pesticides, commodities or pesticide/commodity/country combination. Monitoring data for EBDCs and ETU are from selective surveys, since EBDCs and ETU are not analyzed by FDA's multiresidue methods.

In addition, FDA conducts the Total Diet Study (also called the Market Basket Survey) in which pesticide residues are determined in food prepared for consumption. The Total Diet Study is designed to estimate dietary intake of selected pesticides by various U.S. age-sex groups. Foods are collected four times per year in retail markets at 12 locations throughout the U.S. and are prepared as table-ready (cooked) before analysis. Each market basket consists of 234 foods that represent at least 90 percent of the items in the American diet. Thirteen of the 234 foods are now being analyzed for ETU, however, no results of ETU analyses are available at this time (E. Gunderson, FDA, personal communication, 10/10/89).

The United States Department of Agriculture, Food Safety and Inspection Service (USDA-FSIS) monitors for pesticide and drug residues in meat and poultry as part of their National Residue Program. However, no samples have been analyzed for EBDCs or ETU.

A number of States have pesticide monitoring programs. These programs generally supplement the FDA and USDA monitoring programs. Eight states are now supplying their monitoring data to FDA in the FOODCONTAM data base. Three (CA, FL and NY) of the eight states have been monitoring for EBDCs and/or ETU. The Agency receives regular reports from FOODCONTAM. Monitoring data available at the time the Comments to the EBDC PD 1 were reviewed are described in an Agency memo (Hummel, 7/13/88). Recently the EPA has received additional monitoring data from FDA and the States. Most of the new data are from samples analyzed for EBDC. Very few samples were analyzed for ETU. The recently received monitoring data include the following:

FDA Monitoring for 1988 and 1989
FOODCONTAM Data base (State data from CA, NY and FL)
California Special Survey for EBDC residues

USDA provided summaries of State data, including State Monitoring data from the FDA's FOODCONTAM data base and the California Special Survey for EBDCs. The EPA already had received FDA monitoring data for 1978-1988 and some of the FOODCONTAM data.

All available domestic U.S. monitoring data from FDA and the States from 1985-1989 are summarized in Table II-9. About 1300 domestic U.S. samples were analyzed for EBDCs, but very few samples were analyzed for ETU.

FDA and State monitoring data (1985-1989) were not used for estimating dietary exposure because of the insufficient number of samples that were collected and analyzed for EBDCs and/or ETU. Since EBDCs and ETU are not detected by FDA's PAM I multi-residue analytical methodology, far fewer samples were analyzed by FDA for EBDCs and/or ETU than for other pesticide chemicals, such as

Table II-9

FDA Monitoring Data and State Data for EBDCs and ETU 1985-1989 to date (7/6/89)

Crop	EBDC Residues					ETU Residues				
	Total # Samples	Ave. Res. (ppm)	#ND (0.02ppm)	# Pos.	Max. Res.	Total # Samples	Ave. Res. (ppm)	#ND	# Pos.	Max. Res.
Root Crops										
Carrots	30	0.053	29	1	1.0					
Potatoes	52	0.020	51	1	0.04					
Radishes	2	0.020	2	0						
Beets	5	0.020	5	0						
Beet Tops	2	0.020	2	0						
Turnips	7	0.186	5	2	0.8					
Turnips w/ tops	3	0.020	3	0						
Ginger root	7	0.020	7	0						
Onions	5	0.020	5	0						
Garlic	2	0.020	2	0						
Sugar Beet pulp	1	0.020	1	0						
Leafy Vegetables										
Broccoli	37	0.201	26	11	3.1					
Cabbage	61	0.032	59	2	0.55					
Cauliflower	11	0.064	10	1	0.5					
Brussels Sprout	7	0.045	6	1	0.19					
Celery	30	0.115	24	6	2.0	2	0.002	2		ND
Chinese Cabbage	4	0.215	3	1	0.8					
Bok Choy	3	1.247	2	1	3.7					
Collards	19	0.139	15	4	0.76					
Escarole	1	0.020	1	0						
Kale	11	0.074	10	1	0.61					
Lettuce	126	0.152	117	9	6.0					
Endive	5	0.020	5	0						
Mustard Greens	10	6.413	4	6	54.5					
Spinach	54	1.586	34	20	41.3	12	3.552	3	9	9.22
Kale	6	0.283	5	1	1.6					
Swiss Chard	3	0.020	3	0						
Turnip greens	10	1.347	3	7	5.7					
Kohlrabi	3	0.020	3	0						
Legumes & Grains										
Green Beans	13	0.242	12	1	2.9	1	0.22	0	1	0.22
Beans	1	0.020	1	0						
Peas	11	0.020	11	0		24	0.048	10	24	0.21
Peas, Chinese	5	0.616	4	1	3.0					
Corn on Cob	23	0.020	23	0						
Citrus	66	0.020	66	0		4		4	0	ND

Table II-9, continued

FDA Monitoring Data and State Data for EBDCs and ETU 1985-1989 to date (7/6/89)

	EBDC Residues					ETU Residues				
Crop	Total # Samples	Ave. Res. (ppm)	#ND (0.02ppm)	# Pos.	Max. Res.	Total # Samples	Ave. Res. (ppm)	#ND	# Pos.	Max. Res.
Pome Fruits										
Apples	35	0.071	32	3	0.73	10	0.029	3	7	0.12
Apple Juice Con	2	0.020	2	0						
Pears	12	0.043	11	1	0.3					
Stone Fruits										
Apricots	9	0.020	9	0						
Peaches	5	0.020	5	0						
Nectarines	2	0.020	2	0						
Plums	4	0.020	4	0						
Cherries	5	0.020	5	0						
Cucurbits										
Cantaloupes	27	0.057	26	1	1.03					
Melons	20	0.178	18	2	2.5					
Cucumbers	58	0.044	57	1	1.4					
Squash	64	0.020	64	0						
Other Fruiting Vegetables										
Tomatoes	136	0.054	126	10	1.4	13	0.015	10	3	0.07
Tomatoes (canned)	20	0.089	19	1	1.4					
Peppers	81	0.032	80	1	1.0	1	0.012	0	1	0.012
Eggplant	7	0.020	7	0						
Small Fruits & Berries										
Strawberries	29	0.065	27	2	1.0	8		7	1	0.06
Raspberries	0		0	0						
Grapes	9	0.473	8	1	4.1					
Other										
Mushrooms	16	0.089	13	3	0.68	7	0.101	2	5	0.188
Bananas (import	126	0.036	121	5	1.6					
Almonds	1	0.020	1	0						
Artichokes	1	0.020	1	0						
Asparagus	15	0.020	15	0						
Avocados	1	0.020	1	0						
Mangoes	2	0.020	2	0						
Kiwi	3	0.020	3	0						
Papayas	1	0.020	1	0						
Pineapple	4	0.020	4	0						
Total # samples	1331		1223			82		41		

Averages include non-detectable residues as 0.02 ppm

Averages include ND as 0.002 ppm

captan, which are detected by FDA's PAM I multiresidue methodology. Although a total of about 1300 samples of various foods were analyzed for EBDCs and/or ETU by FDA and the States, no more than 15 samples per commodity were analyzed for both EBDC parent compounds and ETU derived from these compounds. The registrant's monitoring data were not used because those data were determined to be invalid for several reasons such as the limited number of samples tested and the lack of valid storage stability studies. However, the average residues found in the limited data available from FDA and State monitoring studies (including the California Survey for EBDCs) are generally 1 to 2 orders of magnitude lower than the Agency's current exposure estimates. For these reasons, the Agency believes that current residue estimates are likely to overestimate cumulative dietary risk and individual risk on many crops. Once the Market Basket survey data required under the authority of FIFRA section 3(c)(2)(B) are received (September 1990) and reviewed, the Agency will make any necessary adjustments to its dietary risk estimates.

c. Developmental Effects

For acute exposure, the Agency attempts to estimate the maximum likely residue distribution of single day exposures for certain population subgroups. Anticipated Residues for acute exposure were based on the maximum residues or 95th percentile residues from residue field trials, along with processing factors for washing, cooking and commercial processing, as described above for chronic exposure analysis. Adjustment for percent of crop treated is not appropriate for an acute analysis and is not done, because an acute effect may result from exposure to a residue in a single serving. Acute analyses were performed for developmental effects of ETU from the use of each parent EBDC compound. Tables II-10 A, B and C present residue estimates used in acute exposure analyses for maneb, mancozeb, metiram and nabam, respectively.

Table II-10a

Anticipated Residues for Maneb and Maneb Derived ETU for Acute Exposure

Commodity	Residue (ppm) Maneb	Residue (ppm) ETU
Carrots	18.	0.080
washed	9.0	0.080
cooked	9.0	2.4
Potatoes	0.099	0.003
washed	0.049	0.003
baked flesh	0.049	0.17
baked skins	0.049	0.69
baked whole	0.049	0.22
Wet Peel	0.099	0.003
Dry Peel	0.099	0.003
Potato Chips	0.099	0.003
Potato Granules	0.099	0.003
Sugar Beets	2.7	0.004
White Sugar	1.0	0.004
Molasses	1.0	0.004
Dried Pulp	3.5	0.004
Sugar Beet Tops	179	1.7
Turnips	19	0.043
washed	9.5	0.043
cooked	9.5	2.5
Turnip Tops	122	0.68
washed	61	0.68
cooked	61	15
Onions, Green	22	0.040
washed	11	0.040
cooked	11	2.7
Onions, bulb	12	0.16
washed	6.1	0.16
cooked	6.1	1.7
Celery	180	1.3
washed	108	1.3
cooked	108	23
Lettuce, Leaf		1.7
washed	119	1.7
Lettuce, Head	18	0.29
washed	11	0.29
cooked	11	2.4
Spinach	92	0.47
washed	55	0.47
cooked	55	12
Collards	92	0.47
washed	55	0.47
cooked	55	12

Table II-10a

Anticipated Residues for Maneb and Maneb Derived ETU for Acute Exposure (continued)

	Residue (ppm)	
Commodity	Maneb	ETU
Mustard Greens	85	0.20
washed	51	0.20
cooked	51	10
Broccoli, unwashed	48	0.24
washed	29	0.24
cooked	29	6.0
Kohlrabi	48	0.24
washed	29	0.24
cooked	29	6.0
Brussels Sprouts	48	0.24
washed	29	0.24
cooked	29	6.0
Cabbage, untrimmed	16	0.11
Cabbage, trimmed	2.1	0.020
washed	1.3	0.020
cooked	1.3	0.27
Chinese Cabbage	2.1	0.020
washed	1.3	0.020
cooked	1.3	0.27
Cauliflower	2.1	0.020
washed	0.020	0.020
cooked	0.27	0.27
Kale	57	0.32
washed	34	0.32
cooked	34	7.2
Beans, Succulent	11	0.24
Cooked/canned	0.11	1.1
Cooked/frozen	0.80	0.62
Cooked/pureed	0.11	0.80
Cannery waste	15	0.47
Beans, Dry	6.3	0.090
washed	0.44	0.090
cooked	0.44	0.57
Succulent Bean Vines	2140	9.0
Dry Bean Vines	702	14
Peppers	24	0.080
washed	17	0.080
cooked	17	1.2
Tomatoes	12	0.002
washed	8.5	0.002
Wet pomace	7.4	0.025
Dry pomace	4.0	2.4
Canned whole	4.0	0.025
Catsup	4.0	0.025

Table II-10a

Anticipated Residues for Maneb and Maneb Derived ETU for Acute Exposure (continued)

	Residue (ppm)	
Commodity	Maneb	ETU
Tomatoes (cont'd)		
Paste	4.0	2.4
Juice from paste	4.0	2.4
Eggplant see tomatoes		
Cucumber	3.4	0.10
washed	2.4	0.10
cooked	2.4	0.26
Squash	0.95	0.002
washed	0.66	0.002
cooked	0.66	0.044
Melons	2.3	0.015
washed	1.6	0.015
cooked	1.6	0.12
Pumpkin	2.3	0.015
washed	1.6	0.015
cooked	1.6	0.12
Apples	30	0.51
washed	21	0.51
cooked-see applesauce		
Fresh Juice	1.5	0.78
Cooked Juice	1.5	0.64
Wet Pomace	139	2.6
Dry Pomace	388	13.9
Apple Sauce	2.7	0.64
Apple Baby Food	1.5	0.64
Apricots	156	3.9
washed	109	3.9
cooked	109	24
Peaches	175	5.5
washed	122	5.5
cooked	122	6.3
Nectarines	75	2.0
washed	52	2.0
cooked	52	2.3
Grapes	15	0.54
washed	8.4	0.54
cooked	8.4	0.60
Dry Pomace	9.6	1.2
Wet Pomace	9.0	0.75
Thick juice	0.55	7.5
Raisins	4.3	1.4
Raisin Waste	24	2.4
Almonds	2.3	0.010
Almond Hulls	368	0.10

Table II-10a

Anticipated Residues for Maneb and Maneb Derived ETU for Acute Exposure (continued)

	Residue (ppm)	
Commodity	Maneb	ETU
Sweet Corn (K+CWHR)	1.9	0.016
washed	0.13	0.016
cooked	0.13	0.16
Corn Fodder	93	0.24
Corn Cannery Waste	3.8	0.048
Bananas, whole	0.22	0.023
Banana, edible portion	0.050	0.030
Figs	3.2	0.066
Cranberries	0.74	0.012
Papayas	5.2	0.002
Rhubarb	180	1.3
washed	108	1.3
cooked	108	23
Beef Commodities		
Milk	0.21	0.15
Liver	0.44	0.13
Muscle	0.14	0.058
Kidney	0.19	0.12
Fat	0.23	0.019
Poultry Commodities		
Whole eggs	0.014	0.010
Liver	0.11	0.023
Kidney	0.04	0.018
Muscle	0.03	0.011
Fat	0.30	< 0.0016

Table II-10b

Anticipated Residues for Mancozeb and Mancozeb Derived ETU for Acute Exposure

Commodity	Maximum Residue (ppm) Mancozeb	ETU
Apples, Crabapples, Quinces	17	0.32
Washed	11.9	0.32
Cooked	0.68	0.32
Juice	1.8	0.42
Dry pomace	150	
Wet pomace	34	
Pears	31	0.06
Washed	22	0.06
Cooked	22	0.20
Asparagus	0.09	
Washed	0.0063	
Cooked	0.0063	
Bananas	0.71	0.006
Pulp	0.71	
Peel	11.91	0.115
Puree can		
Slices can		
Barley grain	3.1	
Kernel	10.85	0.11
" W/o husk	0.93	0.11
Husk	22.32	0.6
Rough	20.77	0.27
Bran		0.06
Shorts/germ		0.06
Flour		
Sweet corn	0.48	0.02
Corn grain	1.3	0.004
Meal		
Oil		
Flour		
Germ		
Grits		
Hull		
Soapstock		
Oats, rye, wheat grain	1.65	
Bran	3	
Shorts	2	
Flour	1.65	
Bread	0.83	
Fines	8.25	
Overs	11.6	

Table II-10b

Anticipated Residues for Mancozeb and Mancozeb Derived ETU for Acute Exposure (continued)

Commodity	Maximum Residue (ppm) Mancozeb	ETU
Celery, Fennel	3.8	0.018
Trimmed	2.508	0.007
Washed	2.99	0.007
Cooked	2.99	0.32
Carrots	0.66	
Washed	0.33	
Cooked	0.33	
Potatoes	0.1	0.02
Peels	0.18	
Baked flesh		0.022
Baked skin		0.027
Flakes		0.022
Blanched		
Whole baked		
F. Fries		
Peeled		
Chips		
Granules		
Sugarbeets	0.6	0.05
Pulp	1.14	0.02
Molasses	0.02	0.002
Sugar	0.02	0.002
Sugarbeet tops	60	
Cottonseed & Processed prod	1.1	0.11
Cranberry	8.38	0.09
Washed	5.87	0.09
Cooked	5.87	0.128
Grapes	11.4	0.01
Washed	7.98	0.09
Cooked	7.98	0.141
Raisins	21	0.04
Wet pomace	3.65	
Dry pomace	4.79	
Raisin waste	32.49	
Juice		
clear		0.21
Thick		0.32
Pasteurized		0.07
Canned		0.1
Cucumbers	1.8	0.08
Washed	1.26	0.08
Cooked	1.26	0.163

Table II-10b

Anticipated Residues for Mancozeb and Mancozeb Derived ETU for Acute Exposure (continued)

	Maximum Residue (ppm)	
Commodity	Mancozeb	ETU
Melons	3.49	0.05
Cantaloupes		
Watermelons		
Washed	2.44	0.05
Cooked	2.44	0.21
Squash, summer	1.44	0.02
Washed	1.01	0.02
Cooked	1.01	0.086
Onion, bulb	0.48	0.003
Washed	0.34	0.003
Cooked	0.34	
Papaya	33.64	0.4
Pulp		
Canned		
Peanuts	0.14	0.005
Meal		
Oil		
Tomatoes	0.44	0.032
Washed	0.31	0.032
Juice		0.030
Paste	5.4	0.185
Puree	0.39	0.111
Catsup	0.39	0.077
Canned		0.024
Animal products		
Milk	<0.62	0.094
Beef		
Muscle	2.3	0.10
Liver	1.0	0.20
Kidney	0.5	0.13
Fat	0.2	0.06
Eggs	0.02	0.004
Chicken		
Liver	0.01	0.01
Breast	0.01	0.02
Kidney	0.01	0.02
Thigh	0.01	0.02

Table II-10c

Anticipated Residues for Metiram and Metiram Derived ETU for Acute Exposure

Crop	Residue (ppm) Maneb	ETU
Potatoes	0.02	0.17
washed	0.01	0.17
baked flesh	0.01	0.17
baked skins	0.039	0.17
Wet Peel	0.02	0.17
Dry Peel	0.02	0.17
Potato Chips	0.02	0.17
Potato Granules	0.02	0.17
Sugar Beets	0.44	0.21
White Sugar	0.17	0.05
Molasses	0.17	0.05
Dried Pulp	0.58	0.05
Celery *	180	1.3
washed	126	1.3
cooked	126	21.
Tomatoes	1.3	0.05
washed	0.91	0.05
Wet pomace	0.79	0.05
Dry pomace	0.43	0.31
Canned whole	0.43	0.05
Catsup	0.43	0.05
Paste	0.43	0.31
Juice from paste	0.43	0.31
Cantaloupes - washed *	1.6	0.015
cooked	1.6	0.12
Apples	5.4	0.73
washed	3.8	0.73
cooked	3.8	0.75
Fresh Juice	0.27	0.78
Cooked Juice	0.27	0.75
Wet Pomace	25	1.1
Dry Pomace	70	3.1
Apple Sauce	0.49	0.75
Apple Baby Food	0.27	0.75
Sweet Corn (K+CWHR) *	1.9	0.016
washed	0.13	0.016
cooked	0.13	0.14
Pecans	0.02	0.002
Peanuts	0.02	0.07
Meal	0.02	0.04
Oil	0.02	0.04
Peanut Hulls	0.02	0.26
Peanut Vines	50	1.2

Table II-10c

Anticipated Residues for Metiram and Metiram Derived ETU for Acute Exposure (continued)

Crop	Residue (ppm) Maneb	ETU
Animal Products		
Milk	0.05	0.04
Beef Liver	0.14	0.04
Beef Kidney	0.12	0.12
Beef Muscle	0.07	0.05
Beef Fat	0.12	0.05
Eggs	0	0
Poultry Liver	0	0
Poultry Kidney	0	0
Poultry Muscle	0	0
Poultry Fat	0	0

- *Data are translated from maneb, since no recent residue data were submitted for metiram residues on celery, cantaloupe, or sweet corn.

2. Worker Exposure

a. Methodology

Agricultural workers, commercial applicators and homeowners are potentially exposed to ETU through mixing, loading and applying EBDC pesticide products to food and non-food crops and conducting field labor in treated areas. Based on available data, it appears that exposure results primarily from dermal contact. Respiratory exposure is 1-2 percent of the total exposure for non-dust formulations and hence is considered negligible (Lunchick, June, 22, 1988).

The Agency estimated exposure based on surrogate data bases for other pesticides with similar application methods and published literature for dermal and respiratory exposure. For estimating total daily exposure to ETU, respiratory exposure is added to dermal exposure after being corrected for individual EBDC absorption factors. Dermal absorption factors of 9 percent for nabam and 6 percent for metiram were used based on actual measurements in studies on those chemicals. The dermal absorption factor for mancozeb was changed from 1 percent (used in the PD 1) to an upper-bound of 10 percent because of limitations in dosages in the currently available study. For maneb, an upper-bound dermal absorption value of 30 percent (based on an ETU dermal absorption study) was used in the absence of adequate data. See Rispin (August 26, 1988). In addition, the results of metabolism studies for each of the EBDCs were used to calculate their metabolic conversion to ETU. For this assessment, the Agency determined the exposure to ETU and each EBDC encountered by persons doing discrete tasks in the use of an individual EBDC fungicide. The discrete tasks are mixing the spray mixture, loading the pesticide mixture into the spray equipment, applying the spray mixture and ancillary tasks such as flagging for aerial application, or planting treated potato seed pieces. For certain uses when the tasks are performed by a single person, the exposures are combined. Additional data have been required through the March 1989 Data Call-In Notice pertaining to fieldworker exposure.

Available data indicate that the concentration of ETU as a contaminant can vary among products containing the same EBDC and among products containing different EBDCs. Rohm and Haas submitted spray stability data as part of its rebuttal to the PD 1 (March, 1988). These data were evaluated and incorporated into the current exposure assessment. For estimating direct ETU exposure to mixers and loaders from preparing and loading the EBDC spray mixture, the Agency used 0.1 percent of the EBDC exposure estimates for mancozeb and maneb based on the above mentioned study. For estimating direct ETU exposure to applicators, the Agency took into consideration the additional exposure to ETU formed while spraying. Available data indicate that ETU residues increase in the spraying mixtures to 0.2 percent and 6 percent of the amount of mancozeb and of maneb present, respectively. No data for ETU contamination are available for metiram and nabam. For those two EBDCs, the Agency used 0.5 percent for mixer/loaders and 0.6 percent for applicators, as was done in the PD 1. These percentages reflected the percentage of ETU exposure to mixers/loaders/applicators compared to mancozeb that was observed in a mancozeb exposure study. Available data also indicate that the EBDCs and ETU are unstable in tank mix formulations, degrading after being mixed with diluent. Based on these limited data, the Agency assumes that mixer/loader/applicator exposure to ETU is dependent on the percent of ETU present which has been expressed as a percentage of the parent EBDC. In order to more precisely predict mixer/loader/applicator exposure for the ETU breakdown product for each EBDC and respective formulation types, the Agency has required EBDC registrants to submit tank mix stability data for representative end-use products of all formulation types through FIFRA section 3(c)(2)(B). These data are due to EPA in December, 1989.

b. Agricultural Uses

The EBDCs are applied to fruit and vegetable crops to prevent damage by fungi and to protect harvested crops from deterioration. The majority of these uses are pre-harvest and are discussed in more detail in Section III of this document. The EBDCs are also used as a seed treatment for potatoes. Application methods include ground boom, airblast and pressure sprayers.

In the PD 1, the Agency evaluated non-dietary exposure to applicators of mancozeb to apples by airblast and aerial sprays, to onions by ground boom and aerial spray, to potatoes by ground boom, chemigation, aerial and seed treatment and to tomatoes by air, ground boom and hand-sprayers (home gardens). The exposure to mixers/loaders wearing long-sleeved shirts, long pants and chemical-resistant gloves was estimated to be 0.28 mg/lb ai by the dermal route and 4.3 ug/lb ai by the inhalation route of exposure when handling wettable powders (Everhart et al., 1985 and Zogorski and Lafferty, 1985).

Since publication of the PD 1, the Agency has received additional use information and has revised its exposure estimates for workers who apply EBDC products. Based on this information, the assumptions used by the Agency in the PD 1 that ETU exposure to the mixer/loader is 0.5 percent of exposure to the parent compound and for the applicator is 0.6 percent of the parent compound has been changed as discussed in Section II.B.2.a above. Because of the many different crops for which EBDC products can be applied, and certain similarities among them, the Agency selected four crops which it believes represent exposures associated with all other crops and types of application. They are sweet corn, grapes, apples and potato seed pieces. Sweet corn represents row crops and ground boom application, grapes represent airblast application with trellised crops, apples represent airblast application in orchards and potato seed pieces represents preplant treatment of seeds. Exposure estimates assume the use of long-sleeved shirts and long pants during mixing/loading and application and the use of chemical-resistant gloves during mixing and loading. The exposure estimates were based on surrogate data bases and published literature and adjusted for dermal absorption (as previously discussed) when estimating risks. See Lunchick (July 5, 1988). The Agency's dermal and inhalation exposure estimates for sweet corn, apples and grapes are presented in Table II-11.

During ground boom application, the dermal and inhalation exposures to the applicator were estimated to be 4.6 mg/hr and 84 ug/hr, respectively (Lunchick, 1988). These estimates were adjusted to a 1.0 lb ai/A application rate and assume the use of long pants and long-sleeved shirts. Airblast applicator exposure was estimated to be 0.66 mg/lb ai by the dermal route and 1.0 ug/lb ai by inhalation (Zogorski and Lafferty, 1985).

Table II-11

Mixer/Loader/Applicator EBDC and ETU Exposure Estimates for Sweet Corn, Grapes and Apples

CROP	EBDC	DERMAL EXPOSURE (mg/kg/) Daily	DERMAL EXPOSURE (mg/kg/) Annual	INHALATION EXPOSURE (μg/kg) Daily	INHALATION EXPOSURE (μg/kg) Annual
Sweet Corn	Maneb	0.50	2.0	8.6	34
	Mancozeb	0.38	1.5	6.5	26
Grapes	Maneb	0.81	13	4.6	74
	Mancozeb	0.74	11	4.2	63
Apples	Maneb	3.1	22	17.0	120
	Mancozeb	3.1	22	17.0	120

The direct ETU exposures from ETU in the dry formulation and spray mix are as follows:

CROP	EBDC	ETU DERMAL EXPOSURE (μg/kg) Daily	ETU DERMAL EXPOSURE (μg/kg) Annual	ETU INHALATION EXPOSURE (ng/kg) Daily	ETU INHALATION EXPOSURE (ng/kg) Annual
Sweet Corn	Maneb	18	72	340	1400
	Mancozeb	0.61	2.4	11	44
Grapes	Maneb	34	540	56	900
	Mancozeb	1.2	18	4.0	60
Apples	Maneb	130	910	210	1500
	Mancozeb	5.3	37	21	150

(1) Sweet corn

Maneb and mancozeb are applied to sweet corn by ground boom application. The following table presents use information:

Table II-12

Use Practices Information: EBDCs on Sweet Corn

EBDC	Application (Rate lb ai/A)	Acres Treated Daily	Actual Spray Time (hr)	Application Per Year
Maneb	1.6	31	2.9	4
Mancozeb	1.2	31	2.9	4

(2) Grapes

Maneb and mancozeb are also applied to grapes by over-the-vine high pressure sprayers. The high pressure foliage-penetrating spray produces an exposure pattern more analogous to airblast application. The number of applications per year is based on the Agency's estimate of an average vineyard of 100 acres which are treated four times a year. The following is use information:

Table II-13

Use Practices Information: EBDCs on Grapes

EBDC	Application (Rate lb ai/A)	Acres Treated Daily	Actual Spray Time (hr)	Application Per Year
Maneb	2.4	25	2.9	16
Mancozeb	2.0	27.5	3.2	15

(3) Apples

Mancozeb and maneb are applied to apples at an average application rate of 6.5 lb a.i. per acre by airblast sprayers to 36 acres per day. The exposure estimates given in Table II-11 are based on seven applications in an average year.

(4) Potato Seed Treatment

Maneb and mancozeb are used as seed treatments for potato seed pieces. The Agency's exposure assessment is based on a study done using captan, mancozeb and maneb applied to seed pieces at 0.8 lb ai/100 lbs of cut potatoes (cwt). (See Stevens et al., 1980.) Exposure during seed treatment includes filling the duster and cutting and sorting potatoes. Workers were monitored for dermal and inhalation exposure using traditional passive dosimetry techniques. They wore long pants, long-sleeved shirts and jackets. Dusting machine workers wore leather gloves. During the first operation the potato cutting machine was located indoors; during the second operation the cutting machine was located outdoors.

Dermal exposure to workers filling the duster outdoors was 7.5 mg/hr.; inhalation exposure was 0.61 mg/hr. The exposure for workers filling the duster indoors was 1.2 mg/hr for dermal and 0.15 mg/hr for inhalation exposure. The overall weighted means of 10 replicates were 3.1 mg/hr dermal and 0.29 mg/hr inhalation exposure.

There appeared to be no difference in exposure to workers involved with cutting and sorting seed potatoes whether the duster was located indoors or outdoors. The mean dermal exposure to 30 workers was 0.52 mg/hr. This estimate incorporates the study author's assumption of no exposure to the hands because workers cutting and sorting were wearing gloves (i.e., hand exposure from putting on and taking off gloves was not measured). The mean respiratory exposure was 0.039 mg/hr. The exposure values for drivers of tractors pulling the planting rig was 0.37 mg/hr and 0.037 mg/hr for dermal and inhalation exposure, respectively. The observers riding on the rear of the planter had a mean dermal exposure of 0.33 mg/hr and a mean respiratory exposure of 0.027 mg/hr.

Based on data used in the Captan Position Document PD 4 (February, 1989), the entire seed potato treating and planting operation in Maine occurs over five consecutive days. For a two person operation, the Agency estimated that one individual would spend 0.44 hrs/day filling and 8.8 hrs/day cutting.

c. Commercial ornamentals

Maneb and mancozeb are applied to commercial ornamental trees, plants and shrubs by tractor-mounted power hand-held spray guns. The Agency estimates that these pesticides are applied 10 times a year to approximately 6 acres of nursery stock in those nurseries that apply EBDC pesticide products. Two acres are sprayed daily requiring 3 days to treat the nursery once and 30 days to treat it 10 times.

The Agency relied on three surrogate studies (Maddy and Fong, 1983, Abbott et al., 1987, and Copplestone et al., 1976) to estimate worker exposure through the use of EBDCs on nursery stock because no actual exposure data were available. The applicator exposure was estimated to be 43 mg/lb. a.i. by the dermal route and 33 ug/lb. a.i. by the inhalation route. The mixing/loading exposure during commercial ornamental spray operations is expected to be similar to mixer/loader exposure during agricultural uses in that the EBDCs are being added to spray tanks. The Agency evaluated mixer/loader exposure for EBDC use on apples, tomatoes, onions and potatoes. Exposure was estimated to be 0.28 mg/lb ai by the dermal route and 4.3 ug/lb ai by the inhalation route (assuming mixer/loaders wearing long pants, long-sleeve shirts and chemical-resistant gloves). Exposure estimates are presented in Table II-14.

d. Homeowner Lawns and Gardens

Homeowners apply maneb, mancozeb and metiram to vegetables, strawberries, ornamentals, fruit trees and turf by either a compressed air hand-held sprayer or a hose-end sprayer.

Two surrogate studies were used to estimate exposure to homeowners:

1) Kurtz and Bode (Application Exposure to the Home Gardener, American Chemical Society Symposium Series #273, 1985)

measured exposure to gardeners applying carbaryl to vegetables by compressed air sprayers. The mean dermal exposure to individuals adding wettable powders to a compressed air sprayer and applying the spray while wearing long-sleeved shirt and long pants is 120 mg/lb ai. Inhalation exposure was not measured.

2) Chevron Chemical Company, 1988 (in support of the reregistration of acephate). Chevron conducted a study with acephate showing dermal exposure to homeowners using hose-end sprayers while wearing long pants and long-sleeve shirts of 450 mg/lb ai. The inhalation exposure was below detectable levels (0.15 mg/lb ai).

Table II-14

Commercial Nursery Ornamental
EBDC Exposure Estimates

Maneb/Mancozeb to Commercially Grown Ornamentals

Dermal

Mixer/Loader: 0.28 mg/lb ai x 2.4 lb ai/acre x 2.0 acres/day x 170 kg = 0.019 mg/kg/day
Applicator: 43 mg/lb ai x 2.4 lb ai/acre x 2.0 acres/day x 1/70 kg = 2.9 mg/kg/day
Combined Daily: 0.019 mg/kg/day + 2.9 mg/kg/day = 2.9 mg/kg/day
Combined Annual: 2.9 mg/kg/day x 30 days/yr = 87 mg/kg/yr

Respiratory

Mixer/Loader: 4.3 ug/lb ai x 2.4 lb ai/acre x 2.0 acres/day x 1/70 kg = 0.29 ug/kg/day
Applicator: 33 ug/lb ai x 2.4 lb ai/acre x 2.0 acres/day x 1/70 kg = 2.3 ug/kg/day
Combined Daily: 0.29 ug/kg/day + 2.3 ug/kg/day = 2.6 ug/kg/day
Combined Annual: 2.6 ug/kg/day x 30 days/yr = 78 ug/kg/yr

Direct Exposure to ETU in Maneb/Commercially Grown Ornamentals

Dermal

Mixer/Loader: 0.019 mg/kg/day x 0.1% = 0.019 ug/kg/day
Applicator: 2.9 mg/kg/day x 6% = 170 ug/kg/day
Combined Daily: = 170 ug/kg/day
Combined Annual: 170 ug/kg/day x 30 days/yr = 5100 ug/kg/yr
Direct Exposure to ETU in Maneb/Commercially Grown Ornamentals

Respiratory

Mixer/Loader: 0.29 ug/kg/day x 0.1% = 0.29 ng/kg/day
Applicator: 2.3 ug/kg/day x 6% = 140 ng/kg/day
Combined Daily: = 140 ng/kg/day
Combined Annual: 140 ng/kg/day x 30 days/yr = 4200 ng/kg/yr

Table II-14

Commercial Nursery Ornamental
EBDC Exposure Estimates (continued)

Direct Exposure to ETU in Mancozeb/Commercially Grown Ornamentals

Dermal

Mixer/Loader: 0.019 mg/kg/day x 0.1% = 0.19 ug/kg/day
Applicator: 2.9 mg/kg/day x 0.2% = 5.8 ug/kg/day
Combined Daily: = 5.8 ug/kg/day
Combined Annual: 5.8 ug/kg/day x 30 days/yr = 170 ug/kg/yr

Respiratory

Mixer/Loader: 0.29 ug/kg/day x 0.1% = 0.29 ng/kg/day
Applicator: 2.3 ug/kg/day x 0.2% = 4.6 ng/kg/day
Combined Daily: 0.29 ng/kg/day + 4.6 ng/kg/day = 4.9 ng/kg/day
Combined Annual: 4.9 ng/kg/day x 30 days/yr = 150 ng/kg/yr

Table II-15

Homeowner EBDC Exposure Estimates

Maneb or Mancozeb/Homeowner

Dermal

Daily Vegetables: 120 mg/lb ai x 2.6 lb ai/acre x 0.02 acres/day x 1/70 kg = 0.089 mg/kg/day
Annual Vegetables: 0.089 mg/kg/day x 6 days/yr = 0.53 mg/kg/yr

Daily Ornamentals: 120 mg/lb ai x 2.6 lb ai/acre x 0.014 acres/days x 1/70 kg = 0.062 mg/kg/day
Annual Ornamentals: 0.062 mg/kg/day x 5 days/yr = 0.31 mg/kg/yr

Daily Turf: 450 mg/lb ai x 7.6 lb ai/acre x 0.1 acres/day x 1/70 kg = 4.9 mg/kg/day
Annual Turf: 4.9 mg/kg/day x 2 days/yr = 9.8 mg/kg/yr

Daily Fruit Trees: 450 mg/lb ai x 0.12 lb ai/day x 1/70 kg = 0.77 mg/kg/day
Annual Fruit Trees: 0.77 mg/kg/day x 6 days/yr = 4.6 mg/kg/yr

Direct Exposure to ETU in Maneb/Homeowner

Dermal

Daily Vegetables: 0.089 mg/kg/day x 6% = 5.3 ug/kg/day
Annual Vegetables: 5.3 ug/kg/day x 6 days/yr = 32 ug/kg/yr

Daily Ornamentals: 0.062 mg/kg/day x 6% = 3.7 ug/kg/day
Annual Ornamentals: 3.7 ug/kg/day x 5 days/yr = 19 ug/kg/yr

Daily Turf: 4.9 mg/kg/day x 6% = 290 ug/kg/day
Annual Turf: 290 ug/kg/day x 2 days/yr = 580 ug/kg/yr

Daily Fruit Trees: 0.77 mg/kg/day x 6% = 46 ug/kg/day
Annual Fruit Trees: 46 ug/kg/day x 6 days/yr = 280 ug/kg/yr

Direct Exposure to ETU in Mancozeb/Homeowner

Dermal

Daily Vegetables: 0.089 mg/kg/day x 0.2% = 0.18 ug/kg/day
Annual Vegetables: 0.18 ug/kg/day x 6 days/yr = 1.1 ug/kg/yr

Daily Ornamentals: 0.062 mg/kg/day x 0.2% = 0.12 ug/kg/day
Annual Ornamentals: 0.12 ug/kg/day x 5 days/yr = 0.60 ug/kg/yr

Table II-15

Homeowner EBDC Exposure Estimates (continued)

Direct Exposure to ETU in Mancozeb/Homeowner

Dermal

Daily Turf: 4.9 mg/kg/day x 0.2% = 9.8 ug/kg/day
Annual Turf: 9.8 ug/kg/day x 2 days/yr = 20 ug/kg/yr

Daily Fruit Trees: 0.77 mg/kg/day x 0.2% = 1.5 ug/kg/day
Annual Fruit Trees: 1.5 ug/kg/day x 6 days/yr = 9.0 ug/kg/yr

Metiram/Homeowners Roses

Dermal

Daily: 120 mg/lb ai x 0.003 lb ai/day x 1/70 kg = 0.0053 mg/kg/day
Annual: 0.053 mg/kg/day x 10 days/yr = 0.053 mg/kg/yr

Direct Exposure to ETU in Metiram/Homeowners Roses

Dermal

Daily: 0.0053 mg/kg/day x 0.6% = 0.032 ug/kg/day
Annual: 0.032 mg/kg/day x 10 days = 0.032 ug/kg/yr

e. Industrial

The Agency has limited use information on nabam's industrial uses. Two types of loading systems are used: open pour-loading and closed-loading. Of the industrial uses of nabam, only the water cooling systems (tower) and oil well drilling fluids use an open pour-loading system in addition to closed loading systems. The Agency has no exposure data on nabam used in industrial settings. To estimate exposure, the Agency used information from a submission from Alco Chemical Company and Vinings Chemical Company (May 5, 1988, MRID number 014503) that includes the Agency's surrogate data for mixer/loaders open-pouring liquid formulation agricultural pesticides and using closed-loading systems (Lunchick, May 9, 1988).

The contribution of inhalation exposure to total exposure was estimated using data obtained by Maitlen (1982). Maitlen studied various liquid formulations of pesticides which were open poured. The dermal exposure to the mixer/loaders wearing gloves was 2.2 mg/hr when normalized to the 1.0 lb ai/A application rate and the inhalation exposure was estimated to be 45 ug/hr when the material is applied at 1.0 lb ai/A. In comparing inhalation and dermal exposure data during open pouring with protective gloves of liquid formulations in agricultural settings, the Agency estimated based on the Maitlen data that the inhalation exposure was 2 percent of the dermal exposure (Lunchick, June 22, 1988). Dermal exposure during open pour loading was estimated to be:

Cooling Towers: 0.049 mg nabam/kg/day
0.0016 mg ETU kg/day
Drilling Fluids: 0.12 mg nabam/kg/day
0.0039 mg ETU/kg/day

Based on 2 percent of the above dermal exposure estimates, the inhalation exposure to nabam containing microbiocides is as follows:

Cooling Towers: 0.98 ug nabam/kg/day
0.032 ug ETU/kg/day
Drilling Fluids: 2.4 ug nabam/kg/day
0.078 ug ETU/kg/day

(1) Paper mills

According to information received by the Agency (Shema, 1978, McGrew, 1978 and Dowler, 1978), 10 to 50 percent of the total 690 U.S. paper mills use nabam products. Nabam is added as ready-to-use liquids to pulp and paper mill water systems by means of automated pumps. Assuming that the number of paper mills and range of nabam use continues to reflect those figures and one operator at each of the paper plants using nabam is involved in servicing the water system, 70 to 345 operators are potentially exposed. Potential exposure occurs when opening drums, attaching and detaching metering devices and disposing of empty drums. Estimates of the time expended for opening a drum and attaching and detaching metering devices is one to two minutes. Disposal of empty drums requires approximately 15 minutes. Depending on work loads, an operator might handle from one drum every 14 days to two drums per day. Product labels state that operators must wear long pants, long-sleeved shirts, boots, a face shield and rubber gloves when handling the product. Due to the fact that this is a closed system operation, it is assumed there would be minimal exposure occurring during coupling and uncoupling when protective clothing is used. (See Pelletier July 18, 1988.)

(2) Water Cooling Systems

Nabam products are fed into water systems by means of a measuring device attached to product containers (Syssman, 1978 and McGrew, 1978) at a concentration of from three to six ppm. Both open-pour loading and closed loading systems are used. Systems are treated every three to seven days at utility and industrial sites by one operator and at institutional sites by contract service operators who handle from 5 to 20 systems daily. The Agency has no estimates of the number of operators exposed or the number of facilities using nabam products. Exposure occurs when opening drums, detaching and reattaching metering devices, disposing of empty drums and cleaning the system. Time expended for opening a drum and attaching and detaching the metering devices is from one to two minutes. Disposal of empty drums is about 15 minutes and cleaning tasks account for approximately 10 minutes. Product labels state operators must wear long pants, long-sleeved shirts, boots, a face shield and rubber gloves.

Exposure is minimal due to OSHA regulations described earlier, concerning protective clothing requirements for persons applying nabam.

(3) Sugar Mills

Nabam products are added to sugar-cane grinding, crusher and diffuser systems as a metered continuous drip feed to a concentration of 10 to 20 ppm of cane. Approximately 50 percent of the 20 cane mills and 30 beet mills in the United States use nabam. Assuming one operator handles the nabam products, a total of 25 workers are exposed. Exposure occurs when opening drums, attaching and detaching metering devices and disposing of empty drums. Estimated exposure time is 2 minutes for opening the drum and attaching and detaching metering devices and 15 minutes for disposing of empty drums (McGrew, 1978). Product labels state that workers must wear long pants, long-sleeved shirts, boots, a face shield and rubber gloves when handling the product. As this is a closed loading system, exposure is expected to be minimal when correctly using protective clothing. (See DPRA, 1988d.)

(4) Oil Well Drilling Fluids

Little information is available on nabam use practices or exposure potential for this site. The Agency is aware, however, that nabam is added to drilling fluids in open-pour and closed loading systems. Open-pour loading systems provide higher potential exposure to workers than in closed loading systems. It is estimated that five percent or less of the sites use nabam. (See DPRA, 1988d.)

(5) Metal Working Coolant

Although registered for this use, according to two sources (Dowler, 1978 and McGrew, 1978), nabam is not used as an additive for metal working coolants. An alternative chemical, methylene bisthiocyanate, is being used.

C. Risk Characterization

1. Dietary

To estimate dietary exposure and then compare that estimate to a previously determined Reference Dose (RfD), or to estimate potential carcinogenic effect by multiplying by the carcinogen potency factor (Q_1*), the Agency has developed the Dietary Risk Evaluation System, DRES, formerly known as the Tolerance Assessment System (TAS). This computer-based tool is based on consumption patterns derived from a survey conducted by the U.S. Department of Agriculture (1977-78) which involved 3-day dietary records for 30,770 individuals and 3734 food items. The DRES can estimate dietary exposure and risk for the U.S. population and 22 subgroups of the U.S. population. DRES is capable of using "anticipated residues" combined with consumption data as a means of generating a realistic risk assessment. Anticipated residues and percent of crop treated estimates were used in the DRES to estimate dietary risks from residues of EBDCs and ETU in foods.

a. Carcinogenic

Carcinogenic risk due to ETU from dietary exposure is the combination of risk from direct ETU residues plus the risk from ETU formed by in vivo metabolic conversion of the parent EBDC residue. Risks from each of these exposures were estimated for ETU derived from each EBDC parent compound.

In the PD 1, the dietary risk from ETU derived from mancozeb only was estimated because no adequate data were available for other EBDCs. The potential direct dietary risk (not including effects of in vivo conversion) from exposure to ETU based on mancozeb field residue data was estimated to be 5 x 10^{-6}. This was obtained by multiplying the daily estimated exposure to ETU [3.6 x 10^{-5} mg/kg/day], based on consumption estimates from the food factor system and using the percent of crop treated estimates from all EBDCs] by the cancer potency factor for ETU designated as the Q_1* [0.14 (mg/kg/day)$^{-1}$] based on the Innes study. In addition, the Agency also estimated dietary risk of 1.7 x 10^{-5} from exposure to ETU from conversion of mancozeb, in vivo, after eating food containing mancozeb residues. Metabolism studies in rats showed that 50 percent of mancozeb residues were absorbed through the gastrointestinal tract and that 24 mole percent are then metabolically converted to ETU (DiDonato et al., 1985). The in vivo risk estimate in the PD 1 was obtained by multiplying the dietary exposure to mancozeb of 9.7 x 10^{-4} mg/kg/day by 12 percent (50 percent x 24 percent) to yield a dietary exposure to ETU of 1.2 x 10^{-4} mg/kg/day. Multiplying this by the Q_1* yielded a risk estimate of 1.7×10^{-5}. The total potential dietary risk from exposure to ETU from the use of mancozeb on food crops was estimated in the PD 1 to be 2.2×10^{-5}, which was obtained by adding 5×10^{-6} and 1.7×10^{-5}.

Based on the exposure assumptions described in section II.B, EPA has estimated dietary risks for ETU exposure for the maneb and metiram in this PD 2/3 and reestimated dietary risk to ETU from the use of mancozeb. These risk estimates differ from those presented in the PD 1 in that: 1) they are based on crop residue data from maneb and metiram also, and additional crop residue data for mancozeb, 2) the in vivo conversion rate used is 7.5 percent calculated on a weight-to- weight basis (as compared to 12 percent calculated on a mole basis used in the PD 1) based on a recently submitted rat metabolism study and using a molecular weight conversion factor, 3) adjustment corrections were made for washing, trimming and cooking, (4) the new preliminary Q_1* of 0.6 $(mg/kg/day)^{-1}$ was employed and (5) zineb risk estimates are not included (See Hummel memos June 30, 1988 and July 12, 1988.) The combined ETU dietary risk based on direct exposure to ETU residues (not including in vivo conversion) in foods from all EBDC fungicides with registered food uses is now estimated to be 1.1×10^{-4} to the general population. To better approximate actual ETU dietary risk from consumption of foods treated with the EBDCs, the dietary risk estimates from in vivo conversion of EBDCs to ETU were added to the dietary risk estimates for direct dietary exposures to ETU, which results in a combined total risk estimate of 4.0×10^{-4} to the general population. Table II-16 presents ETU risk estimates from direct exposure, *in vivo* conversion and total risk estimates (direct exposure plus *in vivo* conversion) from the use of EBDCs:

TABLE II-16

ETU Dietary Carcinogenic Risks

Chemical	Parent Exp	In vivo ETU Exp	In vivo Risk	Direct ETU Exp	Direct Risk	Total Risk
Mancozeb	.00165	.00091	5.9E-05	.00089	4.0E-05	9.9E-05
Maneb	.00365	.00034	2.0E-04	.00132	6.0E-05	2.6E-04
Metiram	.00038	.00044	2.7E-05	.00017	7.7E-06	3.5E-05
TOTALS			2.9E-04		1.1E-04	4.0E-04

Exp = exposure estimates in mg/kg body weight/day

Although there are currently no food tolerances established for nabam under 40 CFR Section 180, FDA established a secondary direct food additive regulation (21 CFR 173.320) which permits nabam residues of 3 ppm on raw sugar beets or sugar cane from the use of nabam in sugar mill grinding, crusher or diffuser systems. The registrant of nabam has requested voluntary cancellation of all agricultural food and feed uses and sugar beet and sugarcane transport and flume water use.

Because the source of the ETU contribution from individual EBDC chemicals cannot be determined unless the EBDC pesticide used is known, and currently available analytical methods cannot distinguish among the various EBDC fungicides and the EBDC fungicides are often substitutes for one another, dietary risk is considered by the Agency in this risk assessment to be the total estimated risk from ETU (from direct exposure and in vivo conversion) from the use of all EBDCs on the individual crops. See Table II-17 for a listing of estimated ETU dietary carcinogenic risks by individual crop for direct exposure to ETU plus in vivo conversion.

b. Developmental Toxicity

In the PD 1, developmental risk from dietary exposure was not discussed. However, a developmental toxicity risk assessment for this effect was conducted for the Mancozeb Registration Standard (Guidance for the Reregistration of Pesticide Products containing Mancozeb as the Active Ingredient, EPA, April, 1987). Both direct exposure to ETU residues on the crops and in vivo conversion of mancozeb to ETU were considered. To estimate maximum exposure on a given day, maximum residues of mancozeb and ETU were estimated. It was assumed that 100 percent of the crop was treated using all available residue data (not necessarily at the maximum rate). Label PHIs were factored into the analysis. All dietary margins of exposure were found to be above 100 (based on a NOAEL for ETU of ≤ 5mg/kg) for developmental effects for the U.S. population of pregnant women from exposure to ETU from the use of mancozeb on crops.

Table II-17

EBDC Dietary Carcinogenic Risk Estimates from the Use of EBDCs Listed by Individual Crop

CROP	CARCINOGENIC ETU RISK[1]
FIGS[2]	0
PINEAPPLE	$<10^{-10}$
CRENSHAWS	$<10^{-10}$
PECANS	4.0×10^{-10}
FENNEL	9.6×10^{-10}
ASPARAGUS	2.4×10^{-9}
RYE	3.5×10^{-9}
ALMONDS	7.3×10^{-9}
PUMPKIN	1.1×10^{-8}
KOHLRABI	1.3×10^{-8}
PEANUTS[3]	1.6×10^{-8}
EGGPLANT	2.5×10^{-8}
ENDIVE	3.2×10^{-8}
CASABA	5.7×10^{-8}
OATS	5.8×10^{-8}
COTTON	6.4×10^{-8}
FIELD CORN	7.2×10^{-8}
WHEAT	1.1×10^{-7}
HONEYDEW	1.4×10^{-7}
PAPAYAS	1.8×10^{-7}
CAULIFLOWER	2.7×10^{-7}
SWEET CORN[4]	2.7×10^{-7}
BARLEY	3.3×10^{-7}
CANTALOUPE	3.4×10^{-7}

---

[1] Estimates of ETU from use of nabam and zineb on agricultural crops have not been included. For nabam, all agricultural uses have been suspended for several years, there is no known use and registrants have requested voluntary cancellation of all agricultural uses. For zineb, all uses have been suspended since July 1988 and the company holding the technical registration has requested voluntary cancellation of all uses.

[2] Registrant request of September 6, 1989 will eliminate food use on figs, retaining only non-food use. Estimated risk before registrant action was 1.5×10^{-8}.

[3] Estimate assumes that all labels are modified in accordance with the registrant action of September 6, 1989. Previously, estimated risk was 1.3×10^{-7}.

[4] Estimate assumes that all labels are modified in accordance with the registrant action of September 6, 1989. Previously, estimated risk was 3.3×10^{-7}.

Table II-17

EBDC Dietary Carcinogenic Risk Estimates (Continued) from the Use of EBDCs Listed by Individual Crop

CROP	CARCINOGENIC ETU RISK
SQUASH	3.4 X 10^{-7}
SUGAR BEETS [5]	3.7 X 10^{-7}
BRUSSELS SPROUTS	3.8 X 10^{-7}
ONIONS [6]	4.7 X 10^{-7}
CRANBERRIES	5.2 X 10^{-7}
CRABAPPLES	6.1 X 10^{-7}
RHUBARB	6.5 X 10^{-7}
KALE	7.1 X 10^{-7}
GRAPES [7]	9.0 X 10^{-7}
CUCUMBERS	9.2 X 10^{-7}
NECTARINES	1.0 X 10^{-6}
BANANA	1.2 X 10^{-6}
CABBAGE	1.2 X 10^{-6}
PEARS	1.5 X 10^{-6}
POTATOES	1.7 X 10^{-6}
WATERMELON	1.9 X 10^{-6}
LIMA BEANS	2.4 X 10^{-6}
LETTUCE	3.0 X 10^{-6}
PEPPERS	3.4.X 10^{-6}
APRICOTS	6.7 X 10^{-6}
BROCCOLI	1.3 X 10^{-5}
COLLARDS	1.3 X 10^{-5}
SPINACH	1.5 X 10^{-5}
TOMATOES [8]	1.6 X 10^{-5}
MUSTARD GREENS	1.7 X 10^{-5}
TURNIPS	1.7 X 10^{-5}
CELERY	1.8 X 10^{-5}

---

[5] Estimate assumes that all labels are modified in accordance with the registrant action of September 6, 1989. Previously, estimated risk was 1.4 X 10^{-6} .

[6] Estimate assumes that all labels are modified in accordance with the registrant action of September 6, 1989. Previously, estimated risk was 7.1 X 10^{-6} .

[7] Estimate assumes that all labels are modified in accordance with the registrant action of September 6, 1989. Previously, estimated risk was 4.0 X 10^{-5} .

[8] Estimate assumes that all labels are modified in accordance with the registrant action of September 6, 1989. Previously, estimated risk was 2.5 X 10^{-5} .

Table II-17

EBDC Dietary Carcinogenic Risk Estimates (Continued) from the Use of EBDCs Listed by Individual Crop

COMMODITY	CARCINOGENIC ETU RISK
CARROTS	1.9 X 10^{-5}
BEANS	2.5 X 10^{-5}
PEACHES	4.2 X 10^{-5}
APPLES	1.0 X 10^{-4}
TOTAL ESTIMATED RISK FROM CROPS	4.0 X 10^{-4}
MEAT [9]	1.8 X 10^{-7}
MILK (NATIONAL) [10]	5.6 X 10^{-7}
MILK (LOCAL MILK SHED) [11]	1.8 X 10^{-6}
TOTAL ESTIMATED DIETARY RISK	4.0 X 10^{-4}

---

[9] Estimate assumes that all labels are modified in accordance with the registrant action of September 6, 1989. Previously, estimated risk was 1.8 X 10^{-6} .

[10] Estimate assumes that all labels are modified in accordance with the registrant action of September 6, 1989. Previously, estimated risk was 5.6 X 10^{-6} .

[11] Local milk shed dietary risk estimates are a worse case estimate representing small regions where dairy cows may be consuming a diet composed of only EBDC-treated food such as apple pomace from EBDC-treated apples, sugar beet wastes from EBDC-treated sugar beets and other processed food wastes from crops treated with EBDCs.

In the PD 2/3, developmental risk from dietary exposure to ETU from consumption of food treated with EBDC pesticides was estimated by comparing the maximum exposure estimates of each EBDC chemical (mg/kg body wt./day) to the NOAEL from ETU (≤5 mg/kg/day) from a rat teratology study (Khera, 1973). A maximum exposure estimate represents the maximum amount of ETU ingested by a consumer on any given day. The comparison between exposure and the NOAEL is expressed as a Margin-of-Safety (MOS) or Margin-of-Exposure (MOE). An acute dietary exposure analysis using anticipated ETU residues from each EBDC chemical was used to estimate the distribution of single-day exposure for the appropriate population subgroup, which in this case are females of child-bearing age. The analysis assumes that ETU levels occur uniformly within each food commodity at the anticipated residue levels. The following table (II-18) presents estimated average margins-of-safety/margins-of-exposure for consumers of foods treated with EBDCS and presumed to contain ETU residues although metabolic conversion of EBDC to ETU has not been included. For more information see Tomerlin (1988 reviews).

Table II-18

Developmental Toxicity Dietary Risks[1]

	Estimated Average Exposure (mg/kg/day)	Estimated Average MOS/MOE
Maneb	0.006458	770
Mancozeb	0.001003	4985
Metiram	0.001141	4300

---

[1] All agricultural nabam uses were suspended several years ago and registrants have requested voluntary cancellation of all agricultural uses.

c. Thyroid Effects

In the PD 2/3, the toxicology endpoint used in calculating the oral (dietary) reference dose (RfD) for ETU derived from the parent EBDCs was based on thyroid hyperplasia at a Lowest Effect Level (LEL) of 0.25 mg/kg/body weight/day from a 2-year rat feeding study (Graham et al, 1975). A 3000-fold uncertainty factor was used in deriving the RfD of 0.00008 mg/kg/body weight/day. Exposure estimates (ARC) from direct ETU exposure and conversion of EBDC to ETU were calculated from the anticipated residue estimates and corrected for percent of crop treated. Total estimated ETU exposure from each EBDC parent was compared to the RfD for thyroid hyperplasia. The estimate of total ETU exposure for all 55 mancozeb, maneb and metiram food crops was equivalent to 825 percent of the RfD for the general U.S. population, 3313 percent for infants and 1837 percent for children. The estimate of total ETU exposure for the 13 registrant retained food crops is 35 percent for the general U.S. population, 40 percent for infants and 71 percent for children.

d. Conclusions

Although the current estimates of dietary risk are based on the best available data, the Agency believes that the currently available residue data are likely to overestimate dietary exposure and risk for two possible reasons: (1) the residue estimates are likely to be higher than those on the "dinner plate", and (2) the percent of crop treated is not precisely known for sites with low usage. The exposure estimates are based on residue data submitted to support tolerances with some corrections for the effects of commercial processing, washing and cooking.

Field trial data at the maximum registered rate and the minimum PHI, required to support tolerances represent "farm gate" exposure. However, foods are not always treated at the maximum rate nor are they always harvested at the minimum PHI; in many cases, crops are treated at less than the maximum rate, or are harvested several days before the minimum PHI. Additionally, the limited amount of FDA monitoring data available to the Agency suggest in some cases the possibility of lower levels of residues than those found in the field studies even after taking into consideration expected reductions due to commercial processing, washing, cooking and percent of crop treated. The Agency expects that a well-designed and well conducted residue monitoring study could in some cases more accurately estimate ETU residues "at the dinner plate" and could conceivably support different risk estimates which may be one to two orders of magnitude lower than our current risk estimates. The March 1989 EBDC DCI required registrants to design and conduct a market basket study to gather this data and submit the information by September 1990.

EBDC and ETU residues have both been shown to degrade in frozen storage. Frozen storage stability data and limited data on commodities harvested at different PHIs show a decline in EBDC and ETU residues with time in frozen storage and in the field. Ambient and cold storage degradation data for EBDCs and ETU in normal channels of trade could enable the Agency to model degradation rates.

In cases where the percent of crop treated was believed to be less than 10 percent, the Agency used a constant percent of crop treated estimate of 10 percent because of the lack of refined use data. This was true in all cases except for wheat where the Agency had sufficient data to believe the percent of crop treated was in the 1 percent range. Where actual percent of crop treated may be less than 1 percent, the estimated risk for that commodity could be possibly inflated by as much as one order of magnitude. The industry market basket survey could more closely reflect actual usage patterns and may help to further define percent of crop treated in some cases. These data will be considered in the Agency's Final Determination along with any other residue data which the Agency currently has or obtains in response to this or other documents.

2. Mixer/loader/applicator risks

a. Carcinogenic Risks

ETU carcinogenic risk estimates for persons mixing, loading and applying EBDC pesticides range from 10^{-3} to 10^{-7}. These risk estimates are based on current label requirements for mixer/loaders (long pants, long-sleeved shirts, gloves, hat and boots). The addition of protective clothing (coveralls over long-sleeved shirt and long pants, chemical-resistant gloves, shoes, socks and goggles or a face shield and a chemical-resistant apron) may reduce risks to mixers/loaders in excess of 40 percent and applicators in excess of 65 percent. When such protective clothing requirements as specified in the maneb, mancozeb, metiram and nabam Registration Standards and as proposed in this document for maneb, mancozeb, metiram and nabam are factored into these risk estimates, only one carcinogenic risk estimate remains at above 10^{-4}: commercial ornamental applicators using maneb. See Table II-19.

Table II-19
Mixer/Loader/Applicator Carcinogenic Risk Estimates
(incorporating protective clothing*)

MANEB

Site	Application Method	No. Days Exposed	Estimated Excess Carcinogenic Risk		
			M/L	A	C
Apples	Aerial	1	1 E-6	1 E-7	N/A
	Airblast	7	1 E-4	2 E-4	3 E-4
Onions	Aerial	6	4 E-5	4 E-6	N/A
	Groundboom	6	2 E-5	4 E-5	6 E-5
Potatoes	Aerial	4	1 E-4	1 E-5	N/A
	Groundboom	7	2 E-5	4 E-5	5 E-5
	Chemigation	2			4 E-5
	Seed treatment	5			1 E-5
	Fill/cut/plant	5			4 E-6
Tomatoes	Aerial	3	5 E-5	4 E-6	N/A
	Groundboom	7	2 E-5	4 E-5	6 E-5
Sweet corn	Groundboom	4	1 E-5	2 E-5	3 E-5
Grapes	Groundboom	15	5 E-5	1 E-4	1 E-4
Commercial Ornamentals		30	1 E-5	1 E-3	1 E-3
Homeowner	Handsprayer				
Vegetable		6			2 E-5
Ornamental		5			1 E-5
Fruit trees		2			4 E-4
Turf		6			2 E-4

---

* Protective clothing consists of coveralls for mixer/loaders and coveralls and chemical-resistant gloves for applicators. Protective clothing is not factored into homeowner risk estimates.

M/L = mixer/loader
A = applicator
C = combined (mixer/loader/applicator is same person)
N/A = not applicable

Table II-19
Mixer/Loader/Applicator Carcinogenic Risk Estimates (incorporating protective clothing*)

MANCOZEB

Site	Application Method	No. Days Exposed	Estimated Excess Carcinogenic risks		
			M/L	A	C
Apples	Aerial	1	1 E-6	8 E-8	N/A
	Airblast	7	4 E-5	4 E-5	8 E-5
Onions	Aerial	6	2 E-5	8 E-7	N/A
	Groundboom	6	7 E-6	1 E-5	2 E-5
Potato	Aerial	4	4 E-5	2 E-6	N/A
	Groundboom	7	8 E-6	8 E-6	2 E-5
	Chemigation	2			2 E-5
	Seed treatment	5			2 E-5
	Fill/cut/plant	5			2 E-6
Tomatoes	Aerial	3	2 E-5	9 E-7	N/A
	Groundboom	7	8 E-6	1 E-5	2 E-5
Sweet corn	Groundboom	4	4 E-6	3 E-6	7 E-6
Grapes	Groundboom	15	2 E-5	2 E-5	4 E-5
Commercial Ornamentals		30	3 E-6	2 E-4	2 E-4
Homeowner	Handsprayer				
Vegetables		6			4 E-6
Ornamentals		5			2 E-6
Turf		2			8 E-5
Fruit trees		6			4 E-5

---

* Protective clothing consists of coveralls for mixer/loaders and coveralls and chemical-resistant gloves for applicators. Protective clothing is not factored into homeowner risk estimates.

M/L = mixer/loader
A = applicator
C = combined (mixer/loader/applicator is same person)
NA = not applicable

Table II-19

Mixer/Loader/Applicator Carcinogenic Risk Estimates (incorporating protective clothing*)

METIRAM

			Estimated Excess Carcinogenic risk		
Site	Application Method	No. Days Exposed	M/L	A	C
Apples	Aerial	1	9 E-7	4 E-6	N/A
	Airblast	7	2 E-5	1 E-4	1 E-4
Potatoes	Aerial	4	3 E-5	4 E-6	N/A
	Groundboom	7	6 E-6	2 E-5	2 E-5
Homeowner	Handsprayer				
Roses		10			3 E-7

---

* Protective clothing consists of coveralls for mixer/loaders and coveralls an chemical-resistant gloves for applicators. Protective clothing is not factored into homeowner risk estimates.

M/L = mixer/loader
A = applicator
C = combined
+PC = plus protective clothing (coveralls and gloves)

Table II-19

Mixer/Loader/Applicator Carcinogenic Risk Estimates

NABAM

Site	Application Method	No. Days Exposed	Estimated Excess Carcinogenic risk* M/L/A
Cooling Towers	Open-pour	48	4 E-5
	Close-pour	48	5 E-5
Secondary Oil Recovery	Close-pour	48	4 E-5
Oil Well Drilling Fluids	Open-pour	48	1 E-4
Fracturing Fluids	Close-pour	26	6 E-6
Sugar/Paper Mills	Close-pour	26	8 E-5

---

* Risk estimates assumed only protective clothing as specified on the nabam product labels.
M/L/A = mixer/loader/applicator

b. Developmental and Thyroid Effects

Margins-of-safety/margins-of-exposure were calculated for agricultural workers, commercial applicators, industrial workers and homeowners who may be exposed to EBDC pesticide products. Developmental and thyroid MOSs/MOEs were calculated using daily exposure estimates. For mancozeb and metiram where information was available on the parent compound, the developmental NOEL for the parent and the NOEL for ETU were used to calculate the MOS/MOE resulting from exposure to either mancozeb or metiram and to the ETU derived from those parent compounds. For maneb and nabam, the Agency used the developmental study NOEL for ETU ($\leq$ 5 mg/kg/day) and used in vivo conversion of the parent to ETU plus direct ETU exposure to calculate the MOSs/MOEs. Thyroid MOSs/MOEs also were calculated using seasonal exposure estimates for those sites which the Agency considers as having high consecutive exposure scenarios (i.e., grapes, apples and commercial ornamentals). For mancozeb, maneb and metiram, information was available on the parent compound and, therefore MOSs/MOEs were calculated based on exposure to the parent plus direct exposure to ETU (0.25 mg/kg/day). For nabam where there was no information available on the parent, MOSs/MOEs were calculated based on direct exposure to ETU and an in vivo conversion. The Agency believes that although thyroid MOSs/MOEs based on repeated daily exposures represent "worst case", it is prudent to calculate them in this manner due to the fact that these workers may not have time to recover from thyroid effects before their next exposure. The Agency's current data base does not provide a definitive basis for determining a likely recovery period for thyroid effects.

Several MOSs/MOEs were below 100. With incorporation of additional protective clothing requirements as specified in the mancozeb, maneb, metiram and nabam Registration Standards and as proposed as requirements in this document for mancozeb, maneb, metiram and nabam (coveralls over long-sleeved shirts and long pants, chemical-resistant gloves, shoes, socks and goggles or a face shield and a chemical-resistant apron), most MOSs/MOEs increased to 100 or higher. See Table II-20.

c. Conclusions

Assumptions surrounding mixer/loader/applicator developmental and thyroid risk estimates are:

1) Due to the lack of dermal absorption data on the parent compound, an upper-bound estimate of 30 percent absorption factor was used for maneb based on an ETU dermal absorption study. This may overestimate exposure by 3-fold because dermal absorption for maneb is expected to be closer to mancozeb and metiram (between 6-10 percent) as they are structurally similar chemicals. This would increase most MOSs/MOEs (with additional protective clothing) to over 100 except for thyroid effects from maneb used on grapes and commercial ornamentals. See Table II-20. Dermal absorption data have been required for maneb and its ETU degradate through FIFRA section 3(c)(2)(B). These data are due

TABLE II-20

Mixer/Loader/Applicator Developmental and Thyroid MOSs/MOEs
(With full proposed protective clothing)

MANEB

			Margin-of-Safety/Margin-of-Exposure		
				Thyroid	
Site	Application Method	No. Days Exposed	Developmental	Daily	Seasonal
Apples	Aerial				
	M/L	1	1500	-	750000
	A	1	14000	-	150000
	Airblast				
	M/L	7	360	-	21000
	A	7	160	-	230
	C	7	110	-	220
Onions	Aerial				
	M/L	6	670	-	42000
	A	6	8000	-	13000
	Groundboom				
	M/L	6	1600	-	100000
	A	6	640	-	1100
	C	6	460	-	1100
Potatoes	Aerial				
	M/L	4	180	-	17000
	A	4	2900	-	7400
	Flagger	4	830	-	1200
	Groundboom				
	M/L	7	1500	-	82000
	A	7	1000	-	1500
	C	7	620	-	1500
	Chemigation				
	C	2	200	-	67000
	Seed treatment	5	2100	-	150000

TABLE II-20

Mixer/Loader/Applicator Developmental and Thyroid MOSs/MOEs (With full proposed protective clothing)

MANEB

			Margin-of-Safety/Margin-of-Exposure		
				Thyroid	
Site	Application Method	No. Days Exposed	Developmental	Daily	Seasonal
Tomatoes	Aerial				
	M/L	3	300	-	32000
	A	3	3700	-	13000
	C	3	620	-	2100
	Groundboom				
	M/L	7	1700	-	110000
	A	7	750	-	1100
	C	7	520	-	1100
Sweet corn	Groundboom				
	M/L	4	1690	-	188000
	A	4	1000	-	2500
	C	4	630	-	2500
Grapes	Groundboom				
	M/L	15	1400	-	36000
	A	15	600	-	410
	C	15	400	20	400
Commercial Ornamentals					
	M/L	30	16000	-	88000
	A	30	120	-	170
	C	30	120	6	170

TABLE II-20

Mixer/Loader/Applicator Developmental and Thyroid MOSs/MOEs
(With full proposed protective clothing)

MANEB

			Margin-of-Safety/Margin-of-Exposure		
				Thyroid	
Site	Application Method	No. Days Exposed	Developmental	Daily	Seasonal
Homeowner*	Handsprayer				
Vegetable	C	6	3100	-	2400
Ornamental	C	5	4500	-	4100
Fruit trees	C	2	360		270
Turf	C	6	60	-	130

M/L = mixers and loaders
A = applicators
C = one person mixing, loading and applying the pesticide
D = daily exposure
S = seasonal exposure
* = additional protective clothing requirements were not factored into homeowner risk estimates.

TABLE II-20

Mixer/Loader/Applicator Developmental and Thyroid MOSs/MOEs (With full proposed protective clothing)

MANCOZEB

			Margin-of-Safety/Margin-of-Exposure		
				Thyroid	
Site	Application Method	No. Days Exposed	Developmental	Daily	Seasonal
Apples	Aerial				
	M/L	1	170000	-	750000
	A	1	1000000	-	4700000
	Airblast				
	M/L	7	33000	-	21000
	A	7	11000	-	7100
	C	7	8000	-	5400
Onions	Aerial				
	M/L	6	56000	-	42000
	A	6	560000	-	420000
	C	6	100000	-	78000
	Groundboom				
	M/L	6	170000	-	125000
	A	6	56000	-	42000
	C	6	42000	-	31000
Potatoes	Aerial				
	M/L	4	15000	-	17000
	A	4	220000	-	270000
	Flagger	4	40000		45000
	Groundboom				
	M/L	7	170000	-	110000
	A	7	83000	-	54000
	C	7	56000	-	36000

TABLE II-20

Mixer/Loader/Applicator Developmental and Thyroid MOSs/MOEs
(With full proposed protective clothing)

MANCOZEB

			Margin-of-Safety/Margin-of-Exposure		
				Thyroid	
Site	Application Method	No. Days Exposed	Developmental	Daily	Seasonal
Potatoes					
	Chemigation				
	C	2	17000	-	38000
	Seed treatment				
	C	5	200000	-	180000
Tomatoes	Aerial				
	M/L	3	24000	-	36000
	A	3	280000	-	420000
	Groundboom				
	M/L	7	170000	-	107000
	A	7	56000	-	36000
	C	7	42000	-	27000
Sweet corn	Groundboom				
	M/L	4	170000	-	188000
	A	4	83000	-	94000
	C	4	56000	-	63000
Grapes	Groundboom				
	M/L	15	167000	8300	50000
	A	15	42000	2100	12500
	C	15	33000	1700	10000

TABLE II-20

Mixer/Loader/Applicator Developmental and Thyroid MOSs/MOEs
(With full proposed protective clothing)

MANCOZEB

			Margin-of-Safety/Margin-of-Exposure		
				Thyroid	
Site	Application Method	No. Days Exposed	Developmental	Daily	Seasonal
Commercial Ornamentals					
	M/L	30	880000	44000	130000
	A	30	8300	420	1200
	C	30	8300	420	1200
Homeowner *	Handsprayer				
Vegetables					
	C	6	83000	-	62000
Ornamentals					
	C	5	140000	-	120000
Turf					
	C	2	1700	-	3800
Fruit trees					
	C	6	11000	-	8300

M/L = mixers and loaders
A = applicators
C = one person mixing, loading and applying the pesticide
D = daily exposure
S = seasonal exposure
* = additional protective clothing requirements were not factored into homeowner risk estimates.

TABLE II-20

Mixer/Loader/Applicator Developmental and Thyroid MOSs/MOEs
(With full proposed protective clothing)

METIRAM

				Margin-of-Safety/Margin-of-Exposure	
				Thyroid	
Site	Application Method	No. Days Exposed	Developmental	Daily	Seasonal
Apples	Aerial				
	M/L	1	5500	-	750000
	A	1	1200	-	5400
	Airblast				
	M/L	7	1300	-	14700
	A	7	300	-	230
	C	7	240	-	230
Potatoes	Aerial				
	M/L	4	590	-	4800
	A	4	5300		8200
	Flagger	4	870		1200
	Groundboom				
	M/L	7	5700	-	110000
	A	7	1900	-	1800
	C	7	1400	-	1800

TABLE II-20

Mixer/Loader/Applicator Developmental and Thyroid MOSs/MOEs
(With full proposed protective clothing)

METIRAM

				Margin-of-Safety/Margin-of-Exposure	
				Thyroid	
Site	Application Method	No. Days Exposed	Developmental	Daily	Seasonal
Homeowner*	Handsprayer				
Roses	C	10	150000	-	240000

M/L = mixers and loaders
A = applicators
C = one person mixing, loading and applying the pesticide
D = daily exposure
S = seasonal exposure
* = additional protective clothing requirements were not factored into homeowner risk estimates.

TABLE II-20

Mixer/Loader/Applicator Developmental and Thyroid MOSs/MOEs
(With full proposed protective clothing)

NABAM

			Margin-of-Safety/Margin-of-Exposure		
				Thyroid	
Site	Application Method	No. Days Exposed	Developmental	Daily	Seasonal
Cooling Towers	open	48	5700	280	2200
	closed	48	4800	240	1800
Oil Well Drilling	open	48	2300	120	880
	closed	26	21000	1100	15000
Secondary Oil Recovery	closed	48	5900	290	2200
Sugar/Paper Mills	closed	26	1500	75	1100

M/L = mixers and loaders
A = applicators
C = one person mixing, loading and applying the pesticide
D = daily exposure
S = seasonal exposure

to the Agency in May 1990 and will be used to further refine M/L/A developmental and thyroid estimates.

2) Daily exposure estimates used to calculate thyroid MOSs/MOEs may present "worst case" risks because they assume a high level of exposure over a short period of time. This is compared to seasonal MOSs/MOEs which assume a lower level of exposure over a longer period of time.

3) Exposure to ETU was assumed to be linearly proportional to that of the parent EBDC. Based on limited data, the amount of ETU, expressed as a percent of the parent EBDC after 4 hours in a tank mix, varied from 0.1 percent to 0.2 percent for mancozeb to 6 percent for maneb wettable powder formulations. Given the similar pattern of use for the various EBDCs on a given commodity, the difference could, in some cases, result in a difference of up to 60-fold in M/L/A exposure and risk, depending on which EBDC product was used for a particular use. See Firestone (October 14, 1988). Tank mix stability data required by the Agency's March 1989 Data Call-In will be helpful to refine estimates of the ETU breakdown in EBDC products and more accurately define risk estimates. These data are due to EPA in December 1989.

4) Due to the lack of nabam exposure data on industrial use exposure, exposure estimates for nabam's industrial uses were based on agricultural closed and open-pour systems. The open-pour method of transferring agricultural pesticides into spray tanks produces significant dermal exposure even with the use of

protective clothing. The less sophisticated and more variable equipment used in agricultural settings makes its applicability for estimating exposure to industrial sites limited. Data on the use of antimicrobials in industrial settings (oil field uses, pulp and paper mill systems, cooling water systems and metalworking fluids) indicate that worker exposure is minimal. See (Lunchick - Review of Chemical Manufacturers Association Antimicrobial DCI Rebuttal, October 15, 1987). The Agency believes that risk estimates derived from agricultural exposure data may possibly overestimate exposure for nabam's industrial uses. The March 1989 DCI required dermal exposure data on oil well drilling (open-pour systems) and sugar/paper mills (closed systems). These data are due to EPA in March 1990. The Agency will refine worker exposure risk estimates upon evaluation of the required exposure studies.

D. REBUTTAL ANALYSIS

The Agency received comments relating to risks in response to the PD 1. The rebuttal comments and the Agency's responses to the rebuttal comments are contained in the following sections: carcinogenicity, mutagenicity, developmental effects, thyroid effects and exposure. Rebuttal comments are on file in the EBDC Public Docket. All comments received during the public comment period are addressed in this document.

1. Carcinogenicity

Rebuttal Comment:

ETU should not be classified as a Group B_2 carcinogen since the effect only occurs above an exposure threshold.

Agency Response:

Since ETU induces an increased incidence of thyroid follicular cell adenomas and adenocarcinomas in rats and hepatomas in mice, it has been placed in Group B_2 (probable human carcinogen) for carcinogenicity as defined in criterion "a" of the Agency's Cancer Risk Assessment Guidelines. This classification is also supported by positive structure-activity data since several other thyroid inhibitors (i.e. thiouracil and thiourea) have been found to induce hepatomas and/or thyroid tumors in rodents. If the Agency develops a policy on the classification of "threshold" carcinogens and if the registrant is able to show that the induction of thyroid and liver tumors is a threshold phenomenon, the Agency would re-evaluate the weight-of-evidence and the appropriateness of the currently employed method for quantitative risk assessment would occur.

Rebuttal Comment:

The Agency is relying on the same carcinogenicity studies of ETU that it relied upon in the original 1977 Rebuttable Presumption Against Registration which were determined to have several deficiencies.

Agency Response:

The Agency agrees that there are deficiencies in these studies, but due to the nature of these deficiencies (relating to study design), the Agency feels that they do not invalidate the tumor responses seen in the rat (thyroid) and mice (liver) studies. In addition, the new NTP studies provide very strong validation of the observation of tumors in the earlier studies. The NTP studies were conducted more in line with current FIFRA test guidelines. In light of these tumor responses, the weight-of-evidence is sufficient to place ETU in Group B_2 (probable human carcinogen).

Rebuttal Comment:

The Innes mouse study does not meet current standards for a carcinogenicity study.

Agency Response:

The Agency agrees that the Innes (1969) mouse study does not meet current standards for a carcinogenicity study in the mouse and in that sense has certain deficiencies (e.g., insufficient numbers of animals, only one dose tested, no individual animal data and thyroid glands not examined). However, the study provides evidence of a dramatic response (100 percent) in the liver tumor rates in males of one strain of mice and females in the other strain of mice. The registrant for mancozeb has had the slides from this study reread in light of current criteria for classifying liver tumors. Since the incidence of liver tumors in the treated B_6AKF male mice is still 100 percent and the incidence of liver tumors in females of this strain and males and females of the $B_6C_3F_1$ strain are similar to the original incidence of hepatomas as diagnosed by Bionetics, this reevaluation of the liver slides from the Innes study largely reconfirms the original magnitude of response and should have no significant impact on the quantification of risk as already performed by the Agency. A comparison of the results of three evaluations (Bionetics 1968, Willigan 1979, and ICF-Clement 1987) is summarized in Hauswirth (June 16, 1988).

Rebuttal Comment:

Since mouse data were used for calculating the Q_1*, the conversion rate of mancozeb to ETU in the mouse, not the rat, should be used in determining the risk of exposure by various routes to ETU.

Agency Response:

The Agency used the conversion factor for mancozeb to ETU derived from a rat metabolism study for the purposes of risk assessment. This was the only available metabolism study on mancozeb. For the purposes of risk assessment for humans, the conversion factor that should be used is the one that would best approximate the conversion factor applicable to man. The Agency believes it is more appropriate to use the available rat metabolism data rather than to estimate the conversion factor for the mouse.

Rebutal Comment:

A surface area correction should not be done when determining the Q_1* for ETU.

Agency Response:

The Agency's current Cancer Risk Assessment Guidelines support using surface area correction when determining a Q_1* for any substance, including ETU. The Cancer Risk Assessment Guidelines state "in the absence of comparative toxicological, physiological, metabolic, and pharmacokinetic data for a given suspect carcinogen, the Agency takes the position that the extrapolation on the basis of surface area is considered to be appropriate because certain pharmacological effects commonly scale according to the surface area" (Dedrick, 1973; Freireich et al., 1966; Pinkel, 1958). The interspecies extrapolation for carcinogenic effects is accounted for by expressing the dose as mg/squared meter body surface area/day. To modify the rodents' experimental dose to human equivalent dose by surface area assumes that different sized animals are not equally sensitive to equal concentrations. This is based on the observation that smaller animals are more efficient eliminators of the parent compound and/or its metabolites than larger animals. This difference in elimination ability is accounted for by the difference between the species surface area to volume ratio.

2. Mutagenicity

Rebuttal Comment:

ETU is not mutagenic. In 1986, a battery of mutagenicity assays on ETU were submitted to the EPA Toxicology Branch Peer Review Committee for consideration. In addition, results of mutagenicity assays with maneb, metiram, mancozeb and nabam were summarized by the Committee to further evaluate the mutagenic risks associated with ETU exposure. The committee determined that results of available mutagenicity data could not be used as supportive information regarding the carcinogenic potential of ETU.

Agency Response:

The Agency has performed a more recent evaluation of available information on ETU for genetic activity (see Dearfield, July 22, 1988). It was concluded that the body of evidence for ETU suggests that ETU is capable of inducing a variety of genotoxic endpoints. These include responses in gene mutation assays (e,.g., Salmonella and mouse lymphoma assays), structural chromosomal assays (e.g., aberrations in cultured mammalian cells as well as a dominant lethal assay) and other genotoxic effects (e.g., bacterial rec assay and yeast conversion assay). It must be noted that while ETU does induce a variety of genotoxic endpoints which serves as support for mutagenicity concern, ETU does not appear to be a relatively potent genotoxic agent. For example, there are instances where positive and negative results in the same type of mutagenicity assay are reported from different investigators; however, these results may be dependent upon the test conditions in each individual laboratory (e.g., problems in protocol, reporting or use of low concentration levels). Overall, it appears that ETU produces a spectrum of genotoxic effects and provides a basis for a mutagenicity concern for ETU. The mutagenicity concern would provide support in the weight of evidence determination of ETU's carcinogenic potential. The Agency therefore disagrees with the commenter that ETU is not mutagenic.

Rebuttal Comment:

ETU does not pose a genotoxic hazard to mammalian species.

Agency Response:

The Agency disagrees with the commenter that ETU does not pose a genotoxic hazard to mammalian species. See the Agency response to the previous rebuttal comment for discussion concerning the mutagenicity concern for ETU and evidence for a genotoxic hazard to mammalian species. In addition, there are suggestions that urea from ETU may be nitrosated with sodium nitrite at appropriate pH's. As many EBDC-treated products are cooked and consumed, humans may be exposed to ETU as a metabolite and contaminant under conditions where nitrosation in the stomach could occur. Nitrosated ETU and ETU in combination with sodium nitrite have been demonstrated to induce potent genotoxic effects in gene mutation assay and in vivo micronucleus and aberration assays. Therefore, this aspect of ETU genotoxicity may provide an increased concern to humans.

3. Developmental Effects

Rebuttal Comment:

The differences in developmental toxicity potential of ETU in various species can be explained by different rates or extent of metabolism in these species.

Agency Response:

The Agency agrees that differences in the response of various species to the developmental effects of ETU could be due to different rates or extent of metabolism of ETU in these species. If the mouse metabolizes ETU at a faster rate than the rat, one would expect that ETU would be shown to be developmentally toxic in the rat but not in the mouse. The commenter also states that the half-life for elimination of ETU in the cat is 3.5 hours and that the cat possesses a metabolic pathway for ETU not present in the rat. ETU is not developmentally toxic to the cat. The Agency is not certain of the point of the registrant's discussion. If the registrant is suggesting that human metabolism may be more like the cat than the rat, and that differences in metabolism explain the different developmental responses in various species, the Agency does not believe there is sufficient information available to conclude either point. The Agency, as noted, used a metabolic conversion rate which best approximated that factor as applicable to humans. As explained earlier, it believes rat metabolism to be appropriate in this case.

4. Thyroid Effects

Rebuttal Comment:

A threshold exists for the effects of ETU in the thyroid of rats and in the liver of mice.

Agency Response:

The Agency agrees that a threshold may exist for the non-carcinogenic effects of ETU on the thyroid and that a threshold mechanism may exist for the formation of thyroid adenomas and carcinomas in the rat. However, the Agency does not believe that a NOEL for the non-carcinogenic chronic effects of ETU on the thyroid of rats has been demonstrated. Although the Agency agrees that a NOEL for the non-carcinogenic effects of ETU on the mouse liver has been established, it does not agree that a threshold mechanism by which ETU causes liver tumors has been demonstrated. Definitive evidence has not been presented on the mechanism by which ETU causes mouse liver tumors. In the absence of such evidence, the Agency believes it is prudent to assume that mouse liver tumors observed following exposure to ETU lack a threshold for this phenomenon.

Rebuttal Comment:

Rohm and Haas commented that the Agency used the wrong toxicological endpoint for determining the ratio of NOELs for the liver effects of ETU versus mancozeb. "EPA calculated the potential carcinogenic risk for mancozeb based on mouse liver tumor induction by ETU. However, it established metabolic conversion of mancozeb to ETU based on data from another species, the rat."

Agency Response:

The registrant is correct in that the Agency used different endpoints for determining the ratio of NOELs of ETU to mancozeb in the mouse. Nevertheless, the ratio of NOELs for the liver effects of ETU versus mancozeb calculated by the Agency are identical to those reported by Rohm and Haas from the CD-1 mice study (O'Hara and DiDonato, 1985). The ratios for thyroid hyperplasia were stated as ETU:mancozeb at 10 ppm:100 ppm and the ratios for increased liver weights as ETU:mancozeb at 100 ppm: 1000 ppm.

Using these same NOELs determined for the effects of each of these chemicals on the thyroid, the Agency has estimated the same ratios for thyroid and liver effects of ETU and mancozeb.

Rebuttal Comment:

The Agency is not correct in its determination of a NOEL for the effects of ETU on the thyroid in the subchronic ETU rat study conducted by Freudenthal (1977). The commenter states that the NOEL for thyroid effects due to ETU reported in the Freudenthal subchronic study was 25 ppm.

Agency Response:

The Agency disagrees with the commenter. The Agency review dated March 7, 1986 set the NOEL for thyroid effects at 5 ppm based upon an increase in the incidence of thyroid hyperplasia, scored as moderate, seen at the 25 ppm dose level at 60 days but not at 90 days. The Agency believed that the effect at 25 ppm was treatment related due to the scoring of the lesion as moderate and since the effect was not seen in the control group nor in the animals sacrificed at 90 days.

Rebuttal Comment:

ETU does not elicit the same magnitude of an effect in man on thyroid function that it does in the rat. The maneb registrant states that man has a reservoir of T_4 that "is always available to counteract stimulation of the thyroid, while in rodents, inhibition of T_4 synthesis and/or release causes immediate stimulation of the thyroid."

Agency Response:

While the Agency agrees that thyroid function may be controlled somewhat differently in humans than in the rat, a United Kingdom factory worker study concluded that T_4 levels in workers were lowered due to ETU exposure (Smith, 1984). Since the effect of ETU on thyroid function in the human (including its impact on T_4 recovery) is not known definitively, the Agency is relying on the results of rodent studies to extrapolate to the human.

Rebuttal Comment:

Results of health surveys indicate that workers can be exposed for long periods of time to ETU with no adverse effects on thyroid function. The mancozeb registrant has cited two health surveys to support this point: 1) Gorden, C.F., de Fonso, L.R., and Smith, J.M., "A Study of the Thyroid Function (T_3, T_4, TSH) of Workers Involved in the Manufacture and Packaging of Dithane Fungicide Products" (1975) and 2) Braverman, L.E., Lipworth, L. and Charkes, D., "A Health Survey of Workers Involved in the Manufacture and Packaging of Dithane Fungicide with Special Reference to Thyroid Function" (1978). Both studies had been previously submitted by the registrant on August 25, 1978 (Volumes 2 and 5) in response to the 1977 EBDC RPAR.

Agency Response:

Although the Agency agrees in general with the conclusion reached by the registrant on both of these particular studies, a major criticism of these studies is that the level of Dithane or of ETU to which these workers were exposed is not known and, therefore, it is difficult to relate the results of these studies with other exposure scenarios resulting from the use of mancozeb.

5. Exposure

Rebuttal Comment:

The Agency did not correctly calculate the conversion rate of mancozeb to ETU.

Agency Response:

The Agency agrees with the commenter that the conversion from mancozeb to ETU was not calculated correctly. The Agency has applied a molecular weight adjustment of 38% (the molecular weight of ETU is 38% of the molecular weight of the parent EBDC) to its previous calculation of a 20% conversion of EBDC parent to ETU. Therefore, the in vivo exposure to ETU from any administered dose of parent EBDC is approximately 7.5% of the administered dose, or for every 100 mg EBDC administered, 7.5 mg ETU are generated.

Rebuttal Comment:

Due to the distinctions among the different EBDCs (chemical structure and use pattern), dietary exposure data regarding one of the EBDC's cannot always be generally extended to the other EBDCs.

Agency Response:

The Agency agrees that there are differences among the different EBDCs both in terms of the chemical structure and sometimes the use pattern. As a result of the Storage Stability Data Call-In Notices of 3/31/87, the Agency now has crop residue data for maneb and metiram and for ETU derived from these two pesticides. These data have been used to assess dietary exposure to these chemicals. Based on the residue data received, some differences in levels of EBDC parent and ETU in foods are noted. Maneb and maneb-derived ETU residues were generally significantly higher than mancozeb or metiram ETU residue levels. Metiram and metiram-derived ETU residues were generally higher than mancozeb or mancozeb-derived ETU residue levels. Differences in residue levels were generally within one order of magnitude.

There are also similarities among the different EBDCs both in terms of chemical structure and use pattern. The EBDCs all degrade to ETU and can be determined by analytical methods based on carbon disulfide evolution. The formula weights for the monomers of all EBDCs are similar.

Although it perhaps would be preferable to base dietary exposure estimates on residue data from the individual EBDC chemical, when residue data were unavailable for one EBDC, data from other EBDCs were used because the differences in residue levels among the various EBDCs were generally less than one order of magnitude. In this document, this type of extrapolation was done for metiram and metiram-derived ETU on several crops.

Rebuttal Comment:

One registrant (Rohm and Haas) made its own estimates of dietary exposure to mancozeb and ETU using field trial data and the Dietary Risk Evaluation System (DRES). Rohm and Haas states that EPA combined data from all of the EBDC's. The dietary exposure estimates by Rohm and Haas are based on data for only mancozeb. Rohm and Haas then reduced the mancozeb residue estimates to account for the effect of washing, and reduced the ETU residue estimates to account for a one percent conversion of EBDC to ETU during the analysis.

To support the need for correction for the effects of washing, Rohm and Haas submitted (MRID #403819-17) a 1977 survey of homemakers, restaurants and food processors on food processing (washing, trimming and peeling). The study showed that an estimated 99 percent of restaurants, households, and food processors use some type of preparation procedure (washing (soaking), rinsing, peeling, trimming), except that an estimated 93 percent of restaurants use a preparation procedure for apples. Washing (soaking) and/or rinsing is reportedly done by an estimated 97 percent of food processors. According to the study, households wash or rinse >80 percent of each commodity studied except onions. Restaurants wash >85 percent of all commodities studied except onions and corn. Onions and corn are generally peeled and husked, respectively. No data were submitted to support the one percent conversion of EBDC to ETU upon analysis of food crops. Several references to applicator exposure studies were cited.

Agency Comment:

Rohm and Haas appears to have used the same mancozeb and ETU residue field trial data as EPA used in the PD 1, although the EPA accession numbers and/or MRID numbers of the data used by Rohm and Haas were not given as part of their comments. The Rohm and Haas residue estimates, before correcting for washing, trimming and conversion to ETU on analysis are very similar to those of EPA as presented in the PD 1. However, since publication of the PD 1, the Agency has revised its mancozeb and mancozeb-derived ETU residue exposure estimates for mancozeb-treated crops from those residue field trial studies because additional residue data for mancozeb and ETU derived from mancozeb have been submitted. Some adjustments were made for differences in the application rate between the data and registered label rates. EBDCs are generally used at rates close to the maximum registered rate close to harvest. Based on the Agency's experience with data on non-systemic pesticides where multiple applications were used, the application rate used closest to harvest generally has the greatest effect on the residue at harvest.

In the PD 1, the percent of crop treated for EBDCs as a group were the only data available for EPA: data were not available for each individual EBDC pesticide. For the PD 2/3, the percent of crop treated has been broken down for each individual EBDC chemical.

EPA agrees with Rohm and Haas that many crops typically are washed before consumption. In the PD 2/3, EPA has corrected the residue estimates for the effects of washing, based on conservative washing factors (the minimum reduction shown in washing studies rather than the average or maximum reduction).

EPA disagrees with Rohm and Haas that the ETU residue estimates should be adjusted for a one percent conversion during analysis. No data were submitted to support the one percent conversion of EBDC to ETU. The references cited by Rohm and Haas that support such a reduction are for applicator exposure studies rather than for residue studies. The Agency agrees that there may have been a problem with conversion to ETU during analysis in the past, but it believes the problem is largely corrected based on data recently received on other EBDC chemicals that show no significant conversion problems during analysis. Any recently submitted residue studies are not expected to suffer from the problem of conversion of EBDC to ETU during analysis because of improvement in the analytical methods for ETU, including a better understanding of causes of degradation during analysis. In fact, studies submitted by the other registrants (BASF and Pennwalt) do not show any significant conversion of EBDC to ETU during analysis or storage, with the possible exception of tomato commodities. EPA notes that Rohm and Haas residue data on tomatoes from the early 70's showed high residues of ETU, but that Rohm and Haas residue data on tomatoes from the mid 80's reported much lower residues of ETU.

Rebuttal Comment:

The Agency's dietary estimates, except for bananas, should be considered worst case, since the estimates are based on residue data where the crops were not washed, trimmed or peeled before analysis and data for the shortest preharvest interval (PHI) were used. Rohm and Haas points out that levels of both mancozeb and ETU decline rapidly in the field, and that most commodities are stored weeks or months before consumption. Additionally, both mancozeb and ETU are unstable in processed foods and decline rapidly with time.

To support their contention that the exposure estimates are worst case, Rohm and Haas submitted market basket studies and table top studies, including analysis of 1000 samples, showing low residues of both EBDC and ETU. The studies report as an EBDC, any residue responding to the carbon disulfide evolution methods of analysis. See Hummel (July 13, 1988) for a list of the studies, along with their MRID numbers.

Agency Comment:

The same registrant's market basket studies and table top studies were previously submitted to EPA by the EBDC registrants as dietary exposure studies submitted in rebuttal to the 1977 RPAR. The studies were discussed in the EBDC Decision Document of October 14, 1982. At that time, the studies were found to be inconsistent and deficient in design and of questionable value in determining representative exposure to populations potentially exposed to EBDC and ETU residues. The Agency maintains this position regarding the utility of these data. Although the analysis of 1000 samples sounds considerable, very few samples of each commodity were analyzed. Only 2 to 30 samples of each commodity were analyzed, generally 10 to 18 samples per commodity. This was an insufficient number of samples on which to base a dietary exposure analysis. Additionally, only summaries of data were provided and there were no data on sample history for any of the samples. This latter deficiency is particularly significant given the propensity of EBDC and ETU residues to degrade in frozen storage.

FDA and the States have also done monitoring for EBDCs and ETU. These data were discussed in Section II.B.1.b of this document. Approximately 1300 samples were analyzed for EBDC and/or ETU by FDA and the States from 1985 to 1989. FDA analyzed about 100 samples for EBDC and/or ETU from 1978 to 1985. As in the registrant's market basket studies described above, FDA and the States analyzed very few samples of each commodity. No more than 15 samples of any commodity were analyzed for both EBDC and ETU from 1985 to 1989. Very few processed commodities were analyzed. No USDA data are available for EBDCs or ETU. USDA does not monitor for EBDCs or ETU as part of their National Residue Program.

FDA and State monitoring data from 1978 to 1989 for EBDC's and ETU residues were summarized by the Agency. A copy of this summary is included in Hummel (July, 1988; November, 1989).

To obtain additional dietary exposure data, the Agency required registrants of EBDC pesticides to generate and submit residue monitoring data from a market basket survey, through its Data Call-In authority under FIFRA section 3(c)(2)(B). These data are required to be collected in a manner which should preclude the problems of the previous studies. These data are due to be submitted to the Agency by September, 1990.

Rebuttal Comment

A mancozeb registrant submitted two applicator exposure studies and a study of the stability of mancozeb formulations. The studies are:

1. Hickey, K., et al. "Dermal and Respiratory Exposure of Orchard Airblast Sprayer Operators to Mancozeb During Mixing, Loading, and Spraying Operations" (1986).

2. Muma, R. and K. Hickey. "A Comparative Study of the Exposure of Orchard Workers During the Application of Different Formulations of Mancozeb" (1985).

3. **Haines, L.D. "Stability of WP EBDC Spray Slurries and Rate of Ethylenethiourea Formation" (1985).**

Agency Response:

The Agency has reviewed these studies and incorporated pertinent data into its revised exposure assessment presented in section II.B (3)(b) of this document.

Rebuttal Comment:

A mancozeb registrant states that the level of direct ETU exposure derived from their products is less than that used in the Agency's PD 1 document (0.6 percent of the exposure to mancozeb for applicators, 0.5 percent for mixer/loaders). The commenter states that an applicator will be exposed to ETU equal to 0.1 percent of EBDC exposure and a mixer/loader will be exposed to 0.2 percent.

Agency Response:

The Agency reviewed the registrant's data and found agreement between the analysis of the mancozeb formulation for ETU, expressed as a percent of mancozeb, and the ETU exposure to individuals handling mancozeb expressed as a percent of mancozeb exposure. A revised exposure assessment has been conducted which incorporates a direct ETU exposure to mixer/loaders of 0.1 percent of the mancozeb exposure and a direct ETU exposure to applicators of 0.2 percent of the mancozeb exposure. The registrant's data also indicated that applicators handling the maneb wettable powder will receive an exposure of 6.0 percent of the maneb exposure. The 6.0 percent figure has also been used in the revised exposure assessment. The data indicate that mixer/loaders handling the maneb wettable powder received a direct ETU exposure of 0.1 percent of the maneb exposure. This information was incorporated into the revised exposure assessment.

6. Other

Rebuttal Comment:

The Natural Resources Defense Council (NRDC) supports the initiation of the Special Review for the EBDC fungicides and urges the Agency to complete it as soon as possible.

NRDC agrees that the Agency was correct in utilizing mancozeb residue data to initiate the Special Review of all EBDC chemicals.

Agency Response:

Whenever possible, the Agency will use actual field residue or monitoring residue data. For the PD 1, the Agency estimated EBDC dietary risks based on mancozeb field residue data because it did not have acceptable data on the other EBDC chemicals. For the PD 2/3, the Agency has used actual field residue data for maneb, mancozeb and metiram.

Rebuttal Comment:

NRDC suggests that if residue chemistry data submitted by EBDC registrants in response to Data Call-Ins are inadequate, the Agency should suspend the use of those registrations.

Agency Response:

It is the Agency's general policy to suspend product registrations for failure to take appropriate steps in response to a Data Call-In Notice, including but not limited to failure to submit adequate data in response to FIFRA section 3(c)(2)(B) requirements. In examining issues relating to whether a registrant has taken appropriate steps to meet data requirements or the adequacy of data submissions, EPA considers a number of factors, including but not limited to the nature and origin of the problems with the data, the extent to which studies were conducted according to Agency requirements, and the nature of the registrants efforts to generate the data, even if the data turn out to be unacceptable for risk assessment purposes. The Agency did not issue Notices of Intent to Suspend to some EBDC registrants for failure to submit data sufficient for risk assessment purposes based upon its assessment of the registrants' efforts to generate the data. However, some Notices of Intent to Suspend were issued in instances where no data at all were submitted or the effort and/or the conduct of the study was deemed not to be adequate.

Rebuttal Comment:

NRDC has stated that EBDC registrants have not met the burden of proving the safety of existing tolerances. NRDC urges the revocation of all Section 409 tolerances for the EBDCs.

Agency Response:

Within 90 days of issuance of the PD 2/3, the Agency plans to propose tolerance revocation actions consistent with the PD

2/3 proposal. The Agency plans to finalize tolerance revocations, allowing time for lawfully treated produce to pass through.

Rebuttal Comment:

NRDC argued that the Federal Government has not protected consumers from EBDC residues in the diet. The multiresidue methods used by FDA to identify pesticide residues in food cannot detect the EBDCs or ETU, and the methods available for specialized tests are time consuming, of questionable accuracy, and unsuitable for enforcement purposes. In addition, very few samples have been tested for the EBDCs using the specialized methods currently available. GAO indicated that FDA had analyzed only 154 domestic samples for EBDCs between 1978 and 1987. Additionally, the Agency has stated in the mancozeb Registration Standard that the available methods are inadequate for enforcement purposes because none are specific for mancozeb. EPA should not allow the widespread continued use of EBDCs in agriculture when FDA is unable to detect the presence of these residues in food and enforce EPA's tolerances.

Agency Response:

Methodologies for EBDCs and ETU are available in the Food and Drug Administration's Pesticide Analytical Manual Volume II (PAM II). The available methodology for EBDCs analyzes the EBDCs as a group by degradation to carbon disulfide (Keppel method), and thus can be considered a multiresidue method. EPA has received reports of difficulties in using the EBDC and ETU methodology from the State of California Department of Food and Agriculture (CDFA). Although there are some drawbacks to the Keppel method, the Keppel method is the best method known to the Agency for tolerance establishment and enforcement purposes. This method was collaboratively studied (JAOAC 54:528, 1971) and is designated as the official, final action method by AOAC for certain dithiocarbamate formulations (AOAC 14th Edition 6.537). The method is listed as method III in PAM II; and is used by FDA for enforcement purposes. The Agency believes that the Keppel method provides satisfactory results and good reproducible recoveries when used by analysts experienced with the method. For ETU, the Agency recommends the Onley method (AOAC 14th Edition 29.119:554). The Onley method for ETU has been studied collaboratively, is the official, final action method for potatoes, spinach, applesauce and milk, and provides acceptable results when properly validated with recovery and control data.

The Agency agrees that the FDA multiresidue methods available in the Pesticide Analytical Manual Volume I (PAM I) do not detect EBDCs or ETU, and thus FDA and the States analyzed fewer samples for EBDCs than for pesticides which were capable of being detected by the PAM I multiresidue methods. However, EPA has no current policy of requiring that a pesticide be capable of being analyzed by a multiresidue method. The registrants have been required to test the EBDCs and ETU using the FDA PAM II multiresidue methods. The results of some of these tests are now available. Mancozeb, maneb, metiram and ETU were not detected by the PAM I methods.

Regarding the suitability of analytical methods for enforcement purposes, the Agency has required, from the registrants, methodology which is specific for each EBDC pesticide. These data have been required through the Registration Standards and/or Comprehensive Data Call-In Notices for each of the EBDCs. The registrants have reported difficulties in developing specific analytical methodology. In the absence of such specific methodology, the Agency recommends the use of the Keppel method for enforcement purposes. Additionally, the Agency is conducting a Special Review of all EBDC pesticides as a group, partially because of the difficulties of distinguishing among the various EBDCs and because ETU is a common metabolite and degradate of all of the EBDCs and is of significant toxicological concern.

Existence of specific enforcement methodology and ease of use of analytical methodology are not the only criteria used by the Agency in determining registration status or initiation of Special Reviews. If specific analytical methods are developed and replace the Keppel method as the official enforcement method for the EBDCs, FDA will need to use five different methods instead of the one analytical method currently used.

Rebuttal Comment:

A nabam registrant requested that the Agency terminate the Special Review process for nabam. They contended that nabam is used exclusively as an industrial microbiocide and that margins-of-safety associated with these uses are acceptable. They submitted two reports: "Exposure and Risk Assessment for Applicators of Nabam Containing Microbiocides" and "Benefits of Nabam Containing Microbiocides."

Agency Response:

The Agency disagrees with the registrant that EPA should terminate the Special Review of nabam. Nabam has registered industrial uses. The Agency has reviewed the registrant's applicator exposure study and noted that a NOEL of 0.25 mg/kg/day was used in their risk assessment for thyroid toxicity. The Agency disagrees with margins-of-safety/margins-of-exposure calculated using a NOEL of 0.25 mg/kg/day and points out that, in its opinion, a NOEL for the effects of ETU on the thyroid has not been determined (Graham et al., 1975). In this study, an LEL (Lowest Effect Level) was established at 5 ppm (0.25 mg/kg/day).

Information submitted on the benefits of nabam were incorporated into the Agency's risk/benefit analysis of nabam.

III. ASSESSMENT OF BENEFITS AND ANALYSIS OF REBUTTAL COMMENTS

A. ASSESSMENT OF BENEFITS

1. Method of Analysis

The information used to evaluate the benefits of the EBDCs was derived from several sources. These sources include: public comments in response to the PD 1, the registrants, USDA/State Extension Service and research personnel, published State pest control recommendations, scientific literature including the American Phytopathological Society's Fungicide and Nematicide Test Results for the years 1955 to 1987, National Pesticide Information Retrieval System (NPIRS), the USDA/State/EPA 1978 Assessment of EBDC Fungicide Uses in Agriculture, analyses prepared by the Agency staff, a Cooperative Agreement between the Agency and the University of Georgia, and an Agency contractor (Development Planning and Research Associates).

The general approach of this analysis was to evaluate, on the basis of available information, the possible economic impacts of a range of regulatory options including the cancellation of some or all registered uses for EBDC fungicides, or modifications to current methods of use of EBDC fungicides. Cancellation options included an analysis of alternative pest control technologies including non-chemical methods. Chemical alternatives were determined from a listing of registered pesticides. The most probable alternatives to EBDCs were chosen on the basis of cost, efficacy, market availability and the suggested uses by State experts and the Cooperative Extension Service. Future Agency actions or market or marketing decisions by registrants or users could change the availability and use of certain alternatives. Analyses were conducted on major sites/commodities. Analyses on individual sites/commodities were conducted which considered scenarios involving cancellation of combinations of fungicides. These quantitative analyses provide the basis for the benefits assessment presented here and are available from the EBDC public docket.

Benefits in this document are calculated in terms of producer impacts and efficiency impacts. Producer impacts were based on projected changes in production costs, crop yield reductions and quality reductions. Efficiency impacts were calculated for three crops where there are potentially substantial impacts beyond the grower level. Efficiency impacts are defined as society (growers, distributors, consumers and others) costs, or the loss to society of the dollar value of goods and services no longer available as a result of the action. The limits of this analysis include assumptions which were made based on the limited usage information available, limited comparative data on yield and quality factors associated with the use of alternative fungicides and non-chemical control measures, and the limited information on minor use crops. In addition, the Agency assumed that only registered alternatives would be available as chemical replacements for the EBDCs if their registrations were cancelled. This is a conservative approach because new fungicides are being developed and tested on many crops for which EBDCs are registered. For some minor crops such as fennel and many ornamental crops, the Agency has no information on use or on comparative performance. However, the Agency recognizes the potential importance of EBDC use on such minor crops and encourages factual data in support of EBDC benefits or information on other control methods (chemical or otherwise) to be submitted in response to this document.

2. Introduction

Four EBDCs, mancozeb, maneb, metiram, and nabam, have registered fungicidal uses in the U.S. As discussed earlier, all zineb uses have been suspended, the registrant for the technical product has requested voluntary cancellation of all zineb uses and no other registrants have accepted the responsibility to support the registrations. Therefore, EPA concluded that the benefits from zineb use are low and no further quantitative assessment of benefits is presented.

The EBDCs are registered to prevent crop damage caused by fungal pathogens to certain fruit, nut, vegetable, field and ornamental (including turfgrass) crops. They are also registered for use as seed treatments for selected field and vegetable crops, as pre-plant treatments for potato seed pieces, as soil treatments and for home gardens. The sole registrant still holding registrations for use of nabam on agricultural sites has recently requested voluntary cancellation of nabam on all agricultural food sites; these registrations have been suspended for several years and there is no known use of nabam on any agricultural crops. Nabam is registered for use as an antimicrobial pesticide in recirculating water systems, sugar mills, pulp and paper mills, oil recovery systems, adhesives, glues, coatings and paints.

EBDCs are registered for use on over 150 sites. Their broad spectrum of activity and relatively low cost appear to have made them relatively important and widely used fungicides. EBDCs also have a multi-site mode of action (affecting two or more enzyme systems) and are used in some cases in combination with fungicides which have single or limited-site modes of action. This practice is carried out to slow or prevent the development of fungal resistance which has been demonstrated to occur when limited mode of action fungicides are used exclusively. Total usage of the EBDCs in the U.S. has been estimated at 12-18 million pounds active ingredient (ai) per year. The largest crop uses by volume of EBDC applied are apples, cucurbits, onions, potatoes, small grains, sweet corn and tomatoes. The largest crop uses in terms of proportion of the crop treated are apples, cucurbits, lettuce, onions, peppers, potatoes, spinach, as well as some other leafy greens (Table III-1).

Cancellation of all currently registered uses is projected to result in first year foregone benefits to producers of approximately $46 to $75 million from changes in the costs of disease control and in short term losses due to possibly reduced yields. In addition to these losses, efficiency losses are estimated at $90 to $305 million per year. Although these may be

Table III-1

Percent of Crop Treated with EBDC Fungicides [a]

Crop	Maneb	Mancozeb	Metiram
Fruits and Nuts			
Almond	9	NR	NR
Apple	10	35	10
Apricot	4	NR	NR
Banana	10	34	NR
Crabapple/quince	NR	*	NR
Cranberry	10	5	NR
Fig/Caprifig	*	NA	NR
Grape	4	19	NR
Papaya	*	*	NR
Peach/nectarine	4	NR	NR
Pecan	NR	NR	1
Pear	NR	11	NR
Pineapple propagation stock	NR	NA	NR
Vegetables			
Asparagus	*	3	*
Bean(green&dry)	38	NR	NR
Broccoli	15	NR	NR
Brussels sprouts	10	NR	NR
Cabbage	16	NR	NR
Cantaloupe	2	6	1
Carrot	12	12	NR
Casaba melon	2	6	NR
Cauliflower	20	NR	NR
Celery	16	10	10
Collard	90	NR	NR
Corn(sweet)	12	6	1
Crenshaw melon	2	6	NR
Cucumber	6	70	*
Eggplant	<1	NR	NR

---

* = No estimate is available for this site
NA = Not applicable; not applied to growing crop
NR = Not registered
a = Nabam not included because all agricultural uses have been suspended for several years and there is no known use; registrants have requested voluntary cancellation of all agricultural uses

Table III-1

Percent of Crop Treated with EBDC Fungicides (continued)

Crop	Maneb	Mancozeb	Metiram
Vegetables			
Endive	<1	NR	NR
Fennel	NR	*	NR
Honeydew	2	6	NR
Kale	90	NR	NR
Kohlrabi	*	NR	NR
Lettuce	60	NR	NR
Lima beans	38	NR	NR
Mustard green	90	NR	NR
Onion	3	72	NR
Peppers	56	NR	NR
Potato [b]	7	32	4
Pumpkin	30	*	NR
Rhubarb	*	NR	NR
Spinach	48	NR	NR
Squash	2	6	NR
Tomato	8	20	1
Turnip Greens	90	NR	NR
Watermelon	2	6	NR
Field Crops			
Barley	NR	<1	NR
Oats/rye	NR	<1	NR
Wheat	NR	<1	NR
Sugarbeets	2	2	*
Peanuts	NR	4	0
Corn, field	NR	<1	NR

* = No estimate is available for this site.
NA = Not applicable
NR = Not registered.
b = Excluding seed piece treatment

sizable impacts in the aggregate, they represent a small amount relative to per capita food expenditure, even if costs are borne by consumers. However, losses are often borne unequally, and some severe localized losses may be incurred by current users of EBDC fungicides and by some processors of these growers' output. Because of the uncertain impact on yield and quality, these estimated losses in production are somewhat more difficult to predict than the projected increased costs of disease control resulting in a larger range in numerical values. The estimated impacts due to yield and quality losses possibly represent an overestimation because in the long term the grower sector may increase acreage to compensate for expected yield losses, such grower losses may be partially offset by increased commodity prices and use of alternative fungicides which may be registered. In calculating these impacts, it is assumed that only currently registered alternatives or currently accepted non-chemical technology would be available at the time of cancellation. It is expected that for all uses, the burden would be largely borne by the user and/or consumer.

A site-by-site summary of EBDC usage and impacts of cancellation on certain food crops is presented in Table III-2. Therein, information is presented on the major use sites and on the sites with a high percentage of the crop treated with EBDCs. Presented below is a narrative discussion of the results summarized in Table III-2, organized by food crop groupings which currently account for the most usage.

Table III-2
Summary of Usage and Benefits of EBDCs for Selected Sites

Use Significance	Extent of Usage AI/Year 1000 lb($)	Extent of Usage Percent of Site Treated	Key Pests	Availability of Economic Alternatives	Economic Impact of Cancellation Type	Economic Impact of Cancellation Extent	
Carrots	25	20-25	Alternaria leaf spot Cercospora leaf spot	chlorothalonil triphenyltin hydroxide copper fungicides	Cost of treatment	Approximately $125,000	Minor
					Production	Negligible	
					Consumer	Negligible	
Potatoes	3,544	43	Early blight Late blight	chlorothalonil TPTH anilazine coppers	Cost of treatment	$4.4 million increase	Cost increase offset by slightly improved production
					Production	1-2% increase valued at about $4 million	
					Consumer	No net effect	
Onions	810	75	Botrytis leaf blight Downy mildew Purple blotch	chlorothalonil chlorothalonil+metalaxyl iprodione	Cost of treatment	$6.5 million total increase or $70/A. on affected acres. 75% of acreage impacted Production costs increase <5%. About 1% of value of production.	Minor

Table III-2
Summary of Usage and Benefits of EBDCs for Selected Sites (continued)

Use	Extent of Usage		Key Pests	Availability of Economic Alternatives	Economic Impact of Cancellation		
	AI/Year 1000 lb(%)	Percent of Site Treated			Type	Extent	Significance
Celery	175	27-35	Early blight Late blight	chlorothalonil benomyl anilazine coppers thiophanate-methyl	Producers	Possible yield loss up to 14% on affected acres; aggregate costs up to $310,000.	Significant advantages for nonusers. Users would about break even in short run In long run, non-users would dominate production
					Consumers	Price increase up to 8 - 13%. Longer term impacts will be less significant.	Minor impact in food budget
					Welfare Loss	$1.3 to $3.4 million in short run.	Moderate
Lettuce	540	60	Downy mildew	captan coppers metalaxyl	Cost of treatment	Slight reduction on 130,000 acres	Minor impacts
					Production	Up to 11% reduction on current acreage & up to 24% reduction on affected acres when resistent occurs.	Major impacts in second year
					Producer price	Potential 80% increase in price from $12.50/CWT to $17 to $22/CWT or $220 - $430 mil. revenue loss after first year.	Major disruption to market.
					Consumer	Potential increase in retail price in short run from about $0.90 to $1.40 - $1.60. Over long run, effects would be reduced.	Major impacts in the second year. Estimated impacts could be mitigated through regional production shifts and imports changes.
					Welfare Loss	$40 - $204 million	

Table III-2
Summary of Usage and Benefits of EBDCs for Selected Sites (continued)

Use	Extent of Usage AI/Year 1000 lb(%)	Percent of Site Treated	Key Pests	Availability of Economic Alternatives	Economic Impact of Cancellation Type	Extent	Significance
Spinach	80	42	Downy mildew	none	User	Possible shift out of production to alternative crops in affected regions.	Severe local impacts on affected acreage.
					Non-user	Increased price and increased production in other regions would reduce price increase over time.	Unknown
					Producer	Estimated impact of $19 million.	Major
Cole crops (cabbage, broccoli, cauliflower, Brussel sprouts)	270	10	Downy mildew Alternaria	chlorothalonil	No impacts anticipated		
Leafy Greens	150 (if available)	90+	downy mildew powdery mildew Alternaria diseases	none identified	Production	Potential yield loss on affected acres of 50% -100%.	Major
Peanuts	260	4	Leaf spot Rust	benomyl chlorothalonil copper hydroxide thiophanate-methyl TPTH	User	$2.4 million in increased costs potential negligible yield effects.	Minor
Peppers	550	56	Anthracnose Fruit rot Forg eye spot	ziram	Production	Up to 40% yield reduction leading to $23 - $40 mil. reduction in farm gate revenue.	Major
Tomatoes	1,350	25-30	Early blight Late blight	chlorothalonil anilazine coppers ziram	Cost of treatment	$3.2 million increase	Cost increase generally offset by improved production
					Production	5-14% increase on 10-20% of acreage, valued at $3.1 million	
					Consumer	No net effect to consumers	

Table III-2
Summary of Usage and Benefits of EBDCs for Selected Sites (continued)

Use	Extent of Usage		Key Pests	Availability of Economic Alternatives	Economic Impact of Cancellation		
	AI/Year 1000 lb(%)	Percent of Site Treated			Type	Extent	Significance
Cucurbits	2,000	45-55	Downy mildew Gummy stem blight Alternaria Anthracnose Carcospora leaf spot	chlorothalonil benomyl coppers metalaxyl+chlorothalonil triadimefon	Cost of treatment	$8.5-10.5 million increase in aggregate or about $48 per affected acre	Minor
					Production	No impact	
					Consumer	No impact	
Apples	3,500	48	Rust Fly speck Powdery mildew Scab Summer diseases	captan benomyl fenarimol triforine triadimefon	Cost of treatment	$15.25/acre reduction or $4.7 million saving	Minor
					Production	Maximum of 9% loss on affected acres 0.5-1.8% loss overall valued at $5-17 million	Moderate on affected acres Minor overall
					Consumer	less than 1% change in price	Minor
Cranberry	15	15	Fruit rot Twig rot	chlorthalonil	Cost of treatment	About $100,000 per yaer.	Minor
Grapes	300	20-25	Phomopsis Downy mildew Black rot	benomyl triadimefon ferbam coppers iprodione captan	Cost of treatment	-$0.36 to +$10.95 per acre change	Minor
					Production	2-5% reduction East & Midwest <1% of tot. U.S. production $1-3 million reduction in value of output	Minor for total U.S. Moderate for localized areas
					Consumer	None	None
Banana	53 (HI) 9,000-11,000 (Latin Am.)	44	Sigatoka disease	propiconazole tridemorph petroleum oil coppers	Cost of treatment	Cost increase of $300 to $400 per acre or $300,000 to $400,000 in aggregate to domestic U.S.	Minor for domestic U.S.

Table III-2
Summary of Usage and Benefits of EBDCs for Selected Sites (continued)

Use	Extent of Usage		Key Pests	Availability of Economic Alternatives	Economic Impact of Cancellation		
	AI/Year 1000 lb(%)	Percent of Site Treated			Type	Extent	Significance
Sweet Corn	700	19	Blight Rust	chlorothalonil for fresh market corn. No registered alternatives for sweet corn grown for processing.	Cost of treatment	$0.75 per acre treatment cost increase for sweet corn grown in Florida. Total cost increase of $405,000.	Minor
					Production	Yield losses in Midwest (principally Minnesota and Wisconsin). Severe effects of 30% yield loss on 50,000 or more acres 1 year out of 5. 10% yield loss 2 or 3 years out of 5. $1.7-$2.1 million yield loss.	Minor
					Consumer	Probable rise in price of canned and frozen sweet corn (less than 10% price increase) in years with yield losses.	Minor
Small grains	650	0.4	Leaf spot Leaf rust Stem rust Tan spot Glume blotch	triadimefon propiconazole	User	$2.0-$14.3 million increased cost and possible yield losses; 0.2% of crop value; loss of positive returns on affected acres near upper end of loss estimate.	Minor
					Nonuser	Possible increased prices of 1 to 3 cents per bushel (less than 1% price increase).	Minor

3. Food Crops

a. Root/tuber crops

1. Carrots

California, Texas, Florida, Michigan, Wisconsin and Washington are the major carrot producing states. Maneb and mancozeb are registered for control of two major foliar diseases of carrots (Alternaria and Cercospora leaf spots). Alternaria occurs in all carrot growing areas while Cercospora problems are scattered, affecting Texas and Michigan but not California and Florida. EBDCs are recommended and used in all carrot producing areas with an estimated 20 to 25 percent of U.S. carrot acreage or about 21,000 acres treated with EBDC fungicides (USEPA, 1988c). The number of seasonal applications varies with disease pressure in the regions where the crop is grown. State recommendations indicate that three applications usually are made in the Northwest; in California two to three applications may be made; in Florida 10 to 14 applications may be made; and in the Midwest up to 12 applications may be required. A typical mancozeb product would be applied at rates ranging from 1.2 to 1.6 lb ai per acre and maneb at 0.8 to 2.4 lb ai per acre. Alternative fungicides registered for the control of these two foliar diseases include various copper compounds, chlorothalonil and triphenyltin hydroxide. Cultural practices for mitigating disease incidence include: (1) crop rotation, (2) destruction of crop debris, and (3) manipulation of fertilization practices.

The limited data [1] from comparative performance field trials of the EBDCs and alternatives for the control of the diseases of concern indicate that the EBDCs and chlorothalonil, a major alternative, are about equal in disease control and should provide essentially equivalent yields. Severe disease conditions were reported for five of the nine trials; EBDCs gave significantly better disease control and/or yield than no treatment in three out of the five trials, and EBDCs were not tested in one of the five trials and in the other trial the EBDC fungicide was applied at a 14-day interval instead of a 7- to 10-day interval. There was no statistically significant difference between chlorothalonil and the EBDCs in any of the tests. Copper fungicides were included in four of the tests and showed increased disease control over no treatment in three cases and increased yields in one case. Of the major carrot growing states, only Texas lists copper fungicides in its recommendations. One trial included triphenyltin hydroxide (TPTH); mancozeb provided significant disease control over TPTH.

If EBDC fungicides were not available, carrot growers would most likely utilize registered fungicides in conjunction with cultural practices to accomplish disease control. Use of chlorothalonil would increase user costs by an estimated $5.33 per acre where users substitute for maneb and $6.45 per acre where users substitute for mancozeb, due to the current differences in cost of the pesticides (USEPA, 1988c). These cost increases are nominal, representing less than two percent of per acre cash expenses and far less than one percent of gross revenue per acre. In the first year following cancellation, EPA estimates that disease control for all carrot growers could increase by about $125,000 if chlorothalonil is used to replace EBDC fungicides. These cost increases are not considered by the Agency to be a serious threat to the viability of carrot production.

---

[1] Only nine studies were found in the American Phytopathological Society's Fungicide and Nematicide Test Results from 1955 to 1987.

Consumers of carrots and carrot products should not be seriously affected if EBDC fungicides are not available for disease control. The volume and quality of production of carrots is not expected to change as the result of EBDC unavailability. Because the production cost increase is small, growers will most likely absorb the cost increase and consumer expenditures for carrots should be unaffected as the result of a change in the chemicals used for carrot disease control (Table III-2).

2. Potatoes

Three EBDC fungicides (maneb, mancozeb, and metiram) are registered for control of two major foliar diseases of potatoes (early blight and late blight) as well as for control of various fungi which cause decay of planted seed pieces.

For control of the foliar diseases, the fungicides are applied as sprays by means of ground equipment, by aerial equipment and in some instances through various sprinkler irrigation systems. Applications typically commence when disease symptoms are first observed and, depending on disease pressure, continue at five to 14-day intervals. The number of seasonal applications for the eastern United States averages seven. For the north central region, the average number of applications is nine and for northwestern States and California, the average number of applications is four. A typical mancozeb product would be applied at rates ranging from 0.7 to 2.0 pounds ai per acre. It is estimated that about 3.5 million pounds ai of EBDC fungicides are applied four times per year to 550,000 thousand acres of potatoes throughout all major potato growing regions (USEPA, 1988n).

Seed piece treatment operations are carried out by individual growers or farm cooperatives. Seed pieces are treated by means of one of several techniques: a dust hopper over a seed piece conveyor belt, a metering device mounted on a mechanical tuber cutter, a revolving drum treater, and a hand-held sifting device. Usually, eight percent dust formulations are applied at the rate of one pound per 100 pounds of seed pieces (USEPA, 1988n).

Cultural practices for mitigating foliar disease incidence include: (1) maintenance of adequate fertilization and soil moisture to support plant vigor, (2) management of irrigation practices so that foliage dries as rapidly as possible and (3) crop rotation excluding disease susceptible solanaceous crops and their weed relatives. In regard to resistant varieties, resistance is usually specific to certain fungal strains; also varieties resistant to one disease are usually susceptible to one or more other diseases. In areas where computerized disease forecasting services are available, the application of treatments according to predictions of disease outbreaks can reduce the frequency and rates of application compared to programs of scheduled applications at regular intervals.

Table III-3 presents a use matrix for alternative registered pesticides for the control of the two foliar diseases and as seed piece treatments.

Table III-3

Alternative Fungicides Registered
for Use Against Various Potato Diseases

Fungicide	Foliar Diseases		Seed Piece Treatment
	Early blight	Late blight	
anilazine	x	x	
Bordeaux mixture	x	x	
chlorothalonil	x	x	
cooper sulf. basic	x	x	
copper ammon. carb.	x	x	
copper resinate		x	
copper oxide	x	x	
copper hydroxide	x	x	
copper oxychloride	x	x	
copper oxych. sulfate	x	x	
formaldehyde			x
metalaxyl + chloroth.	x	x	
streptomycin			x
thiophanate-methyl			x
thiabendazole			x
triphenyltin hydroxide	x	x	

Source: NPIRS search, Registration Division label files, and EPA Compendium of Acceptable Uses.

The Agency reviewed one hundred and twenty foliar potato disease field trials which compared the disease incidence and/or yield differences between EBDCs, alternative fungicides and untreated controls. The analysis of field trials did not include data from tests demonstrating non-statistically significant differences because (1) no disease incidence occurred to challenge the treatments, (2) disease incidence occurred too late in the season to have an impact on yield or (3) large variation among treatment replicates due to situations such as inundation of some plot replicates. In addition, the simultaneous occurrence of more than one disease limited the depth of analysis which could be conducted on the available field trial data. However, taking these factors into consideration, evaluation of the available data were made. In 17 trials in which late blight occurred, chlorothalonil provided significant yield increases compared with untreated controls and in 72 trials in which late blight occurred, EBDCs provided significant yield increases compared with untreated controls. There were no significant yield differences between the EBDCs and chlorothalonil in nineteen trials in which late blight occurred. Copper fungicides, TPTH and anilazine, while significantly better than no treatment; however, the resulting yields were lower than those obtained from the use of chlorothalonil or the EBDCs.

In the 32 field trials reviewed in which early blight occurred, chlorothalonil and the EBDCs produced statistically significant data yield increases over no treatment.

Chlorothalonil provided higher yields than EBDCs and either chlorothalonil or EBDCs provided higher yields than copper fungicides, TPTH and anilazine. However, the highest yields were provided by a combination of metalaxyl and chlorothalonil with slightly lower yields by a combination of metalaxyl and mancozeb. Overall, the following conclusions can be made for potato early and late blight disease control: (1) the EBDCs and chlorothalonil are more efficacious than their alternatives; (2) chlorothalonil combined with metalaxyl is somewhat more effective than the EBDCs; and (3) the various copper fungicides are the least viable alternatives. The copper fungicides and TPTH are often reported to be phytotoxic and damaged foliage may result in lower yields.

For control of potato seed piece decay, approximately 30 field trials were evaluated by the Agency. The data reviewed indicated that when there is sufficient disease pressure, all the registered chemicals provide increased yield over the non-treatment although the compounds that are tested do not always rank consistently in the degree of control. Therefore, no impacts on yields are expected if use of EBDCs on potato seed piece treatments is cancelled.

The major alternative to EBDCs for foliar disease control is chlorothalonil. If all acres currently treated with EBDCs are treated with chlorothalonil, both treatment cost and yield would be expected to increase. Cost would increase by about $2 per treatment acre or $8 per acre, based on the current cost of chlorothalonil. This represents an annual increase in production cost of $4.4 million. Depending on the region, yield could increase by one to two percent valued at more than $4 million per year. In net, the overall impact to users would be minimal because increased treatment costs would be offset by increased revenue from higher yields (Table III-2).

b. Onions

Mancozeb and maneb are registered for disease control of onions. It is estimated that about 810,000 pounds ai of EBDCs are applied to 90,000 to 95,000 acres or 75 percent of onion acreage in all onion growing regions.[2] Mancozeb is used on about 70 percent of onion acreage while maneb is used on about five percent of the acreage (USEPA, 1988k). Mancozeb is registered for control of Botrytis leaf blight, downy mildew, neck rot and purple blotch diseases of onions. Maneb is not used as extensively on onions and is registered for control of Botrytis leaf blight, downy mildew, and purple blotch.

There is a paucity of performance data available to compare EBDCs to other fungicides. One trial against downy mildew showed that there was no significant difference between mancozeb and copper hydroxide in onion yields, but both were significantly better than no treatment. A study of purple blotch control indicated that mancozeb and chlorothalonil provide statistically similar yields, but that iprodione was significantly better than either of the other two fungicides. EBDC fungicides reportedly failed to control Botrytis leaf blight in New York in an area where onion monoculture prevails, but in a Florida trial, EBDC provided better disease control (32 percent yield increase over no treatment) compared with chlorothalonil (16 percent yield increase over no treatment) and copper hydroxide (16 percent yield increase over no treatment). Benomyl provided similar yields to that of mancozeb. Two reports indicating consecutive applications of chlorothalonil can suppress onion yields were noted, it was concluded that if used judiciously with other fungicides it can be useful in a disease management program (USEPA, 1988k).

---

[2] Major onion producing areas are California, the Northeast, North Central States and the Pacific Northwest.

In the absence of EBDCs, chlorothalonil or a chlorothalonil/ metalaxyl combination are likely efficacious alternative chemical controls for the diseases of concern. Other EBDC substitutes include copper hydroxide and iprodione which will control purple blotch, Botrytis leaf blight, and probably neck rot, a disease caused by another Botrytis species.

EPA has estimated that without EBDCs, based on current chemical costs, disease control will cost an average of an additional $70 per affected acre. This estimate is based on an average of 4.5 applications which would cost an average of $15 per acre per application. In aggregate, for onion growers production costs would increase by $6.5 million per year. This represents less than a five percent increase in production costs or about one percent of the value of production. A grower cost increase of this magnitude most likely would cause a minor increase in the price of onions to consumers.

c. Leafy vegetables

1. Celery

Mancozeb, maneb, and metiram are registered to control the two major foliar diseases of celery (early blight and late blight). It is estimated that about 175,000 pounds ai of EBDCs are used on about 10,000 to 13,000 acres or 27 to 35 percent of domestic celery acreage. Chlorothalonil is also widely used with about 25 percent (or less than 10,000 acres) being treated annually (USEPA, 1988d). Some growers may alternate using chlorothalonil and an EBDC fungicide. The fungicides may be applied by means of ground or aerial equipment or by means of sprinkler irrigation systems at three to 14-day intervals depending on disease pressure. In Florida, the fungicides may be applied as often as twice weekly for 20 to 30 times per season. Typically EBDC products are applied at 1.6 pounds ai per acre.

Benomyl, chlorothalonil, anilazine, various copper fungicides, dichlone, ferbam, sulfur, thiophanate-methyl, thiram, and ziram are registered for these uses and are EBDC alternatives.

Certain cultural practices (crop rotation, planting of resistant varieties) can mitigate disease occurrence, but these practices cannot control the diseases below the economic threshold where chemical pesticides are considered necessary to insure that a grower can produce a marketable crop.

The Agency reviewed available field studies conducted between 1955 and 1986. Five studies provided yield information on control of late blight by EBDCs and alternatives. A Least Significant Difference was calculated from the estimated variance between yields reported in the five tests. There was no statistically significant difference in yield between EBDCs and the other fungicides tested: benomyl, chlorothalonil, anilazine, thiophanate-methyl, thiabendazole and basic copper sulfate.

On the other hand, the four studies on early blight did indicate statistical significance between fungicide treatments. Mancozeb provided significantly higher yields than benomyl, thiophanate-methyl, chlorothalonil, anilazine and basic copper sulfate. In addition, benomyl and thiophanate-methyl are subject to having fungi develop resistance to their effects. On the approximately 10,000 acres affected by early blight, yield losses from substituting chlorothalonil (the next best alternative) for the EBDCs could result in an estimated 9 to 14 percent yield reduction compared to the yield expected with EBDC use (USEPA, 1988d). No economically significant yield losses are anticipated from late blight.

The Agency estimates if EBDC fungicides were no longer available, growers would spend about $310,000 or over $30 per acre for alternatives fungicides. In addition to the increase in treatment cost, total U.S. production is estimated to decline by 2.2 to 3.4 percent because the alternative fungicides provide less effective control for early blight. This could cause the farm gate price of celery to increase by 9 to 14 percent or $0.97 to $1.36 per cwt. (hundred weight). For growers who currently use EBDC fungicides to control early blight, revenue is estimated to fall by as much as $7 million or over $70 per acre due to increased production costs and reduced yields. However, total revenue for celery growers in aggregate could increase by $16.4 to almost $22 million due to higher price received for the commodity. At the consumer level, the price of celery could increase by 8 to 13 percent. It is estimated that the efficiency loss or net loss to society would be between $1.3 to $3.4 million per year if EBDC fungicides were no longer available to domestic celery growers (Table III-2).

2. Lettuce

Maneb is registered for foliar use on lettuce for control of downy mildew. Fungicide applications are made at seven to 14-day intervals using ground equipment and less often applications are made by aerial means. It is estimated that 540,000 pounds ai of maneb are applied to 130,000 acres of lettuce (USEPA, 1988i). This represents about 60 percent of the lettuce acreage. Approximately 90 percent of EBDC usage is in California. Arizona and Florida are the next two largest states in terms of EBDC usage, each with less than four percent.

Cultural practices such as crop rotation and weed control practices to eliminate those weed species which serve as disease hosts are recommended to reduce disease incidence. Commercial varieties resistant but not immune to downy mildew are available.

Mildew resistant varieties in some instances become susceptible due to development of new strains of the causal fungus. Alternative registered fungicides for control of downy mildew are captan and various copper compounds.

Limited comparative performance data for downy mildew control which was available from the open literature, indicate that maneb, captan and copper sulfate generally, but not in all cases, reduce the incidence of disease. When the trial results were statistically analyzed, maneb provided significantly better disease control to that given by captan and copper compounds. In trials with metalaxyl, all showed significantly superior disease control to any of the other alternatives including the EBDCs. However, the Agency is aware of fungicidal resistance problems with metalaxyl through California's request for an Emergency Exemption (section 18 of FIFRA) to apply fosetyl-al because resistance to metalaxyl has already occurred in some California lettuce fields. Although metalaxyl provides control for downy mildew, the Agency believes that fungal resistance is likely to develop in fields using metalaxyl within the first year after cancellation of the EBDCs and is likely to become widespread in one to five years if not used in combination with fungicides having a multi-site mode of action.

The USDA/States/EPA Assessment (1978) noted that comparative performance testing showed copper fungicides caused phytotoxicity (yellowing of wrapper leaves and necrotic leaf spots) which would reduce the marketability of treated lettuce. The exact loss would depend upon the quality of other lettuce available at the time of harvest. After consultation with a plant pathologist from the California Cooperative Extension Service working with lettuce, EPA estimated that yield losses along the California coast where downy mildew may be severe, could range up to 25 to 30 percent if EBDC fungicides are not available (USEPA, 1988i).

The economic losses associated with cancellation of EBDC registrations are separated into impacts the first and subsequent years. Based on available data, EPA has estimated that in the first year after cancellation current users of EBDCs would be able to substitute alternative fungicides, such as metalaxyl and copper with possibly some quality losses and no quantity losses. Based on past fluctuation in price due to quality, the reduction in quality due to cancellation of EBDC registrations is assumed by the Agency to bring about an overall five percent price decrease for lettuce which could reduce net revenue (total sales of lettuce minus costs of production) from $263/acre to $95/acre. The relatively better quality lettuce from growers who do not need to control downy mildew is likely to increase in price which may in aggregate offset the losses incurred by current EBDC users who may not be able to control downy mildew without EBDCs. The Agency has made a very conservative assumption, which may prove not to be true, that no additional alternatives will become available in subsequent years. Based on this assumption, EPA has projected that yield could decline by as much as 24 percent for current users as more growers are unable to use metalaxyl due to fungal resistance. However, the downy mildew fungus also may become resistant to fosetyl-al if it becomes registered for use on lettuce. If the downy mildew fungus becomes resistant to metalaxyl and no other effective alternatives are available, the Agency estimates an overall reduction in yield of 5 to 11 percent. As a result of this yield reduction and the highly inelastic demand for lettuce, the farm gate price of lettuce is estimated to increase by 37 to 80 percent and the retail price of lettuce could increase by 34 to 72 percent.

Depending on how well acreage adjusts, the loss to society is estimated at $40 to $204 million per year when resistance to alternative fungicides sets in (Table III-2). The upper bound of impacts is based on no adjustment in the number of acre grown. The lower bound is based on acreage adjustments without changing the proportion of affected and unaffected acres. If acreage grown could shift to unaffected regions, the overall impact could be further reduced. It is difficult to estimate the extent of regional shifts in production because some of the most affected regions, such as the central coast of California, are the primary producing regions of lettuce during certain time periods each year.

3. Spinach

Maneb, the only EBDC fungicide for spinach, is registered for the control of two foliar diseases of spinach (downy mildew and white rust). It is applied as foliar sprays or dusts by ground equipment or by aerial means. Applications begin when the disease is first evident and, depending on disease pressure, continue at seven to fourteen day intervals. An average of 4.5 seasonal applications are made in Texas, Maryland, and Virginia. One or two applications are made in California. Maneb formulations are applied at rates ranging from 1.2 to 2.4 pounds ai per acre. It is estimated that about 80,000 pounds ai of maneb are applied annually to about 17,000 acres of spinach. The two largest spinach producing States are California and Texas each with approximately 25 percent of the acreage. Other major producing States include New Jersey (7 percent), Oklahoma (6 percent), Colorado (5 percent), and Tennessee (5 percent). It appears that about 75 percent of spinach is grown for the processing market.

Non-chemical cultural practices consisting of a three year crop rotation, using disease free seeds and planting resistant varieties can mitigate disease incidence, but, in the opinion of experts contacted by the Agency, none of these controls the diseases of concern at a level to prevent significant economic losses from downy mildew and white rust (USEPA, 1988p). Even resistant varieties suffer yield and quality losses when there is a heavy disease pressure and environmental conditions favor outbreaks of disease.

In addition to maneb, various copper compounds are registered for control of downy mildew; only one of the copper materials is registered for control of white rust as well as downy mildew. None of the leading spinach producing states recommends copper fungicides for spinach, presumably because copper fungicides may cause phytotoxicity to spinach as well as other leafy vegetables. Coppers cause yellowing and necrotic spotting of leaves and thus their market place acceptance is low.

Only two reports of field evaluations of maneb and alternatives for the control of downy mildew and white rust could be found in the Fungicide Nematicide Trial Results between 1955 and 1986. There were no comparisons between maneb and copper compounds. The reports available indicated that maneb provided the best control and was preferred over potential alternatives. A plant pathologist contacted did not know of any trials using copper fungicides to control downy mildew and/or white rust of spinach and did not know of any use of copper fungicides to control these spinach diseases (USEPA, 1988p).

According to experts contacted by the EPA, in the absence of EBDCs, much of the spinach crop grown over winter would not be marketable because of the yield and quality losses from using no fungicides or from using copper fungicides. If this acreage has no other economic use, the loss is estimated to be about $27.5 million per year. Even if all the affected acres are idle, some production can shift to marginal land where spinach has not previously been grown over winter. Assuming 30 percent of the winter crop is grown elsewhere, the economic losses fall to $19 million. In all likelihood, most former users would shift out of spinach to the next most profitable crop. This could reduce the impact further; however, there are insufficient data to estimate this impact (Table III-2).

d. Cole crops

Cole or crucifer crops include broccoli, Brussels sprouts, cabbage, cauliflower, Chinese cabbage, collards, kale, kohlrabi and mustard greens. Cabbage, broccoli, Brussels sprouts, and cauliflower comprise 80 to 85 percent of the cole crops grown in the U.S. While California grows the majority of U.S. cole crops, no one State dominates cabbage production and many States produce cole crops, especially for local market. Over the last ten years, annual usage of maneb is approximately 270,000 pounds ai for the four primary cole crops and, as much as, 150,000 pounds ai for leafy greens when available.

Maneb is registered to control downy mildew and Alternaria leaf spot on these crops. Both plant diseases can reduce quality as well as, directly or indirectly, reduce production. Several copper fungicides, chlorothalonil, metalaxyl, ziram and ferbam are registered alternatives to control downy mildew on several of the crops, in particular, cabbage, broccoli and cauliflower. Copper fungicides tend to be phytotoxic to the crop and therefore are not frequently used. Ziram and ferbam are not widely available and are not recommended by State Extension Service agents. Metalaxyl is registered only for cabbage, cauliflower and broccoli. Resistance by the downy mildew fungus to metalaxyl can develop unless it is used in combination with a multi-site mode of action fungicide. Therefore, only chlorothalonil or chlorothalonil combined with metalaxyl are viable alternatives for EBDC fungicides to control downy mildew on cole crops.

Alternaria leaf spot is often controlled with the same fungicide application used to control downy mildew. The major alternative chemical control is chlorothalonil; cultural controls include crop rotation, weed management, and irrigating early in the day to reduce surface moisture.

Comparative fungicide trials reported in Fungicide and Nematicide Test Results were reviewed for data on both diseases, 25 trials for downy mildew and 7 trials for Alternaria. Only two studies contained yield data and both showed no significant yield differences between maneb and chlorothalonil. Maneb, chlorothalonil and metalaxyl significantly reduced disease incidence; in only one trial did maneb give significantly better disease control compared to chlorothalonil. However, metalaxyl gave significantly better control than maneb or chlorothalonil alone, but metalaxyl must be combined with either maneb or chlorothalonil to prevent development of fungal resistance. The nine trials which included copper fungicides indicated that copper fungicides provide equal or sometimes better disease control than maneb although phytotoxicity due to copper was noted in the studies. Because alternatives will be available for the primary cole crops, loss of EBDC fungicides should have little or no impact on downy mildew or Alternaria leaf spot control. For the remaining cole crops (kale, collards, mustard greens, turnip greens, and turnips) there are no viable alternative fungicides.

Consequently, the loss of EBDC fungicides would have a major impact.

If registrations of EBDC fungicides were cancelled, EPA estimates that all broccoli, Brussels sprout, cabbage, and cauliflower acreage currently being treated with maneb would most likely be treated with chlorothalonil. On a per treatment basis, chlorothalonil currently is more expensive than maneb, but maneb is applied more frequently than chlorothalonil (two versus five applications on average according to experts contacted by the EPA). When considering total application costs, chlorothalonil use is less expensive than maneb. Therefore, costs to growers are expected to decline by less than one percent, causing a negligible change in net farm income. As a result of the negligible impact to growers, no market nor consumer impacts are anticipated (Table III-2).

On leafy greens, EBDC fungicides are the only viable control for leaf spot causing diseases. EBDC fungicides are currently available for use in Georgia and Tennessee through Special Local Need registration and a Emergency Exemption, respectively. There may be some existing stocks of maneb [3] labelled for these crops being used in the southeastern U.S. When available, virtually the entire crop of collards, kale, mustard greens, and turnip greens would be treated with EBDC fungicides.

---

[3] Use on this crop had previously been deleted from the registered technical maneb label.

In states where there is little or no EBDC fungicide available, such as Texas, an unquantified number of growers have reportedly lost their second of two cuttings. Consequently, yields on affected acres have declined by fifty percent. All acreage is not likely to be affected in any given season; therefore, the yield impact to the overall crop may be less than fifty percent. However, the impact to growers and the processors of leafy greens are expected to be significant.

e. Peanuts

Metiram is registered to control Cercospora leaf spot (early leaf spot) and mancozeb is registered for rust and Cercospora leaf spot. It is estimated that 260,000 lb ai of mancozeb are used to treat about four percent of the U.S. peanut acreage. Metiram is rarely, if ever, used on peanuts (University of Georgia, 1988). Applications are made by means of ground or aerial equipment or through various sprinkler irrigation systems. Application commences when disease symptoms first become apparent and, depending on disease pressure, continues at seven to 14 day intervals.

Non-chemical cultural practices and the planting of resistant varieties can mitigate disease incidence; however, none of the practices directly controls the diseases of concern. Crop rotation with grass crops, sanitation and early planting can delay the appearance of the foliar diseases and thus permit a delay in commencement of fungicide applications. There are no commercially available varieties which are immune to one or more of the diseases. Programs which monitor environmental conditions favorable for disease development can suggest critical periods of fungicide applications and possibly reduce the number of applications.

Alternative fungicides registered for control of Cercospora leaf spot and rust include chlorothalonil, benomyl, copper hydroxide and sulfur. Additionally, various copper compounds and thiophanate-methyl are registered for use against the more prevalent leaf spot diseases. Where benomyl or thiophanate-methyl are suggested for use, it is recommended that it be alternated or tank mixed with a fungicide that is not prone to the development of fungal resistance.

Fifty-nine field trials comparing disease control and yield impacts resulting from early and/or late leaf spot were reviewed. Based on the analysis of the comparative efficacy data of the chemicals registered for control of early leaf spot, rust, and complexes of these diseases: (1) chlorothalonil is superior in control and yield to EBDCs and other fungicides tested; and (2) among the EBDC fungicides, mancozeb is somewhat superior in performance to metiram, and maneb is the least effective. Developing resistance of the leaf spot fungi to benomyl and thiophanate-methyl is indicated by the progressive loss of efficacy over the span of years for which efficacy tests were reported. Among the copper fungicides, copper oxychloride appeared to be the least effective and copper resinate the most effective. Sulfur applied as a single active ingredient was the least effective fungicide and was reported to cause phytotoxicity.

The Agency has assumed that EBDC fungicides would be replaced with chlorothalonil if EBDC registrations were cancelled. Peanut growers in the Alabama, Florida and Georgia would be virtually unaffected by loss of EBDCs because of their limited use of EBDCs and high dependence on chlorothalonil. Late leaf spot, which is controlled by chlorothalonil, but not EBDCs, is a problem in these states. However, growers in Virginia, Oklahoma and Texas where late leaf spot causes less concern, depend more on EBDC fungicides. It is estimated that growers in Virginia, Oklahoma and Texas would pay higher prices for disease control based on current differences in chemical costs. It is estimated that the impact would be $2.4 million annually (Table III-2).

f. Peppers

There are approximately 60,000 acres of peppers grown in the U.S. Florida and California are the two largest pepper producing states. North Carolina, Georgia, and New Jersey also are major pepper producing states. There is little EBDC usage in California whereas in Florida, Georgia, and New Jersey virtually all of the pepper acreage is treated with EBDC fungicides. In total, it is estimated that 50 to 60 percent of domestic pepper acreage is treated with EBDC fungicides.

EBDC fungicides are used to control anthracnose, early blight, and fruit rot. Currently, there is no economically viable alternative fungicide registered for the primary fungal diseases affecting the pepper crop. Consequently, significant short term impacts are expected if EBDC fungicides were no longer available. If additional acreage is not readily available, production could fall by as much as 40 percent and farm gate price would increase by about one third from $31 to $42 per cwt. It is estimated that if acreage could increase, output would fall by 28 percent and farm gate price would increase by about 24 percent from $31 to $38 per cwt.

If EBDC fungicides are cancelled the loss to all growers would be between $22.6 to 39.8 million dollars per year. Consumer expenditure on peppers would increase significantly and the total loss to society or efficiency loss would be between $49 and $98 million per year (Table III-2).

g. Tomatoes

Tomatoes for both the fresh and processed market are treated with EBDC fungicides. Approximately 1,350,000 pounds ai of EBDC fungicides are applied to 100,000 acres of tomatoes. The Southeast treats almost all of the tomato acreage with EBDCs. The Midwest region treats up to 60 percent, the Northeast treats up to 83 percent, and California treats up to 9 percent of its tomato acreage (USEPA, 1988r).

Mancozeb, maneb and metiram are registered for the control of up to six foliar and fruit diseases of tomato listed in Table III-4. The fungicides are applied by means of ground or aerial equipment or through sprinkler irrigation systems. Applications typically commence when disease symptoms are first observed and are repeated every five to 14 days as long as disease pressure remains. The average number of seasonal applications ranges from four in California to 22 in Florida. Alternative fungicides registered for the control of six tomato diseases are also given in Table III-4.

Sixty-seven comparative performance evaluations of fungicides for control of the diseases of concern provided indications of disease control and the impact on yield. Because most trials were conducted against varying complexes of tomato diseases, and there was varying degrees of disease severity among tests, a statistical analysis of the data was not possible. EPA estimated the percentage yield lost or gained when chlorothalonil was substituted for the EBDCs. The average yield changes were calculated from average treatment yields from field tests conducted in given regions and reported in the annual publication, Fungicide and Nematicide Test Results. The EPA estimated average percentage yield change resulting from a substitution of chlorothalonil for EBDCs for the Southeast was a yield increase of 5.5 percent, for the Northwest a 14 percent increase and for the Midwest an 8 percent increase. Less than half of the field trials analyzed included captan, ziram, various copper compounds, and anilazine. These fungicides generally were less effective and provided lower yields than chlorothalonil and the EBDC materials.

Table III-4

Fungicides Registered for Control of Tomato Diseases

Fungicides	Disease					
	Early Blight	Late Blight	Gray Leaf Spot	Gray Leaf Mold	Septoria Leaf Spot	Anthracnose
Mancozeb	x	x	x	x		x
Maneb	x	x	x	x	x	x
Metiram	x	x	x			x
Zineb	x	x	x	x	x	x
Anilazine	x	x	x	x	x	x
Benomyl				x		
Bordeaux mixture	x	x		x		x
Captan			x		x	x
Chlorothalonil	x	x	x	x	x	x
Copper oxide	x	x	x		x	x
Copper oxychloride	x	x				x
COCS [1]	x	x			x	x
Copper sulfate	x	x			x	x
Copper ammon. carbonate	x					
Copper resinate	x			x	x	
Copper hydroxide	x					
Dichloran				x		
Dichlone	x	x				
Ferbam	x			x		x
Metalaxyl [2]		x				
SDMC [3]	x	x			x	x
Thiram		x	x			
Ziram	x				x	x

[1] Copper oxychloride sulfate
[2] In combination with mancozeb
[3] Sodium dimethlydithiocarbamate

Sources: NPIRS search, Registration Division label files, EPA Compendium of Accepted Uses

The Agency estimated that cancellation of registration of EBDC fungicides would result in total replacement of EBDCs by chlorothalonil. Annual treatment cost per affected acre would be projected to increase by $4.87 per acre due to the current differences in chemical costs. The cumulative cost increase in all regions is estimated to be $3.2 million with the greatest impact in the Southeast ($1.9 million), followed by the Midwest ($0.6 million), California ($0.4 million) and the Northeast ($0.3 million). However, Agency estimates of percentage yield changes were determined for EBDC usage shifting to chlorothalonil based on field tests conducted in several regions of the U.S. Yield increases for the acreage under high disease pressure where growers shift to chlorothalonil are expected to range from five to 14 percent depending on the growing region. The value of these yield increases for the Southeast is estimated to be $1.9 million and $0.4 million for each of the other three regions. Therefore, the projected value of the yield increases ($3.1 million) nearly offsets the projected increased price of substituting chlorothalonil for EBDC fungicides (Table III-2).

h. Cucurbits

Cucurbits are members of the gourd family and include squash, pumpkins, cucumbers, cantaloupes, watermelons, and other melons. The Agency review focused on the five cucurbits listed above; however, most characteristics, such as, primary diseases, relative usage, and alternative fungicides should apply to the remaining cucurbits with EBDC registrations. Maneb, mancozeb, and metiram are registered to control some or all of the following: Alternaria leaf blight, angular leaf spot, anthracnose, Cercospora leaf spot, downy mildew, gummy stem blight, Pythium fruit rot, and scab. Angular leaf spot is caused by a bacterial pathogen; the other diseases are caused by fungal pathogens. These pathogens may attack the foliage and/or the fruit and may reduce yields or quality.

The major alternative to the EBDC fungicides is chlorothalonil, although benomyl, metalaxyl and triadimefon are used in combination with the EBDCs or chlorothalonil to supplement control of specific diseases. Copper compounds are sometimes essential for the control of angular leaf spot. As an alternative to (or for use in conjunction with) chemical control, some disease resistant varieties of cucurbits have been developed. These varieties have greater resistance to specific diseases and so require lower chemical rates and/or fewer fungicide applications.

Fungicides are used extensively on cucurbit crops in all producing States with most acres receiving multiple treatments in a given year. The estimated annual usage of EBDCs on the five cucurbits reviewed is 1.2 million to 2.9 million pounds ai per year with about 40 percent of the acres receiving some form of EBDC application (DPRA, 1988b). Essentially all fresh cucumbers are treated with EBDCs.

If the registrations of EBDC fungicides are cancelled, the cucumber industry would be the most severely affected of the five cucurbit market analyzed. As a result of replacing EBDC's with chlorothalonil, treatment cost would increase by about a $4.5 million per year. Estimated impacts to the five cucurbit markets due to loss of EBDCs are based on the relatively higher cost of replacement chemicals which range from $8.5 million to $10.5 million annually (DPRA, 1988b). See Table III-2. No yield impacts are anticipated.

i. Apples

Metiram, maneb, and mancozeb are registered for use on apples to control several important diseases (Table III-5). Scab is considered the most important of these diseases, although several of the so called "summer diseases" of apples not only can reduce the value of fresh market apples, but can result in deterioration of fruit in storage. Fungal diseases of apples can appear and spread rapidly throughout an orchard and can result in upwards of 70 percent crop loss if the diseases are untreated. Diseases of apple are most important in eastern orchards, moderately important in north central region and least important in western orchards. Use of EBDC fungicides to control apple diseases reflects this pattern with treatment of approximately 67 percent, 22 percent and 3 percent of the apple acreage in these regions, respectively (USEPA, 1988a).

The major alternatives to EBDC fungicides include captan, benomyl, dodine, copper fungicides, fenarimol, triforine and triadimefon. Although there are alternatives for each of the listed diseases for which the EBDCs are registered, no one of

Table III-5
Fungicides Registered for Control of Certain Apple Diseases

Fungicides	Summer Diseases									Other Diseases		
	Bitter Rot	Frog-eye Leaf spot/ Black Rot	Blotch	Botyro-spheria Rot	Brooks Spot	Brown Rot	Bulls-eye Rot	Fly-speck	Sooty Blotch	Scab	Cedar Apple Rust	Quince Rust
Mancozeb	x	x				x		x	x	x	x	
Maneb	x	x		x			x	x	x	x	x	x
Metiram	x	x		x		x		x	x	x	x	
Benomyl								x	x	x		
Bordeaux Mixture	x	x	x							x		
Calcium polysulfides		x	x							x		
Captan	x			x	x		x	x		x	x	x
Copper oxy-chloride sulfate		x								x		
Copper sulfate	x	x	x		x		x		x	x		
Dichlone										x		
Dodine										x		
Fenarimol										x	x	
Ferbam	x	x	x		x	x		x	x	x	x	x
Glyodin										x		
Sodium polysulfides										x		
Sulfur		x				x			x	x	x	x
Thiophanate-methyl	x									x		
Thiram		x	x	x	x	x		x	x	x	x	
Triadimefon											x	
Triforine										x	x	
Ziram							x			x		

these fungicides is a universal substitute for the EBDC fungicides (Table III-5). For example, fenarimol and triadimefon will not control the summer diseases. In addition, resistance to benzimidazole fungicides (benomyl and thiophanate-methyl) has developed in some apple orchards, thus eliminating their use in some orchards and reducing their use in others. Concern has been expressed that the apple scab fungus and other fungi also may become resistant to certain systemic fungicides such as fenarimol, triforine and triadimefon. Due to their multi-site mode of action, EBDC fungicides are often relied upon to prevent or slow the development of fungicide resistance to certain other fungicides.

Many states recommend inclusion of EBDCs into an apple grower's integrated pest management (IPM) program to control apple scab. Some growers or various organizations monitor climatic conditions and amount of fungal spores present to enable growers to spray orchards only when conditions are conducive to fungal infection and thus reduce the number of fungicide sprays applied. Some apple varieties have been produced which are resistant to apple scab; however, consumer acceptance of new apple varieties is slow and development of a new apple orchard to the bearing stage is expensive and requires several years.

Usually, control of both cedar apple rust and quince rust is accomplished with the same fungicides and in conjunction with scab controls. Use of EBDCs generally prevents economic loss from rusts, whereas captan would provide much lower protection and benomyl provides none at all. Economic losses would be expected if captan and/or benomyl were used for rust control on apples. The systemic fungicides are very effective and would also prevent economic loss. If EBDCs are not available and if under the unusual circumstances that the systemic fungicides could not be applied at the proper time due to weather or fungal resistance, poor control under heavy disease pressure could result in yield losses that year and premature defoliation. Defoliation which would affect the following year's fruit production. After consulting plant pathologists in apple growing areas, the Agency estimates that losses would not exceed 10 percent of the crop; losses with current controls generally range from one to two percent (USEPA, 1988a).

If the EBDCs were no longer available for summer disease control, combinations and variations of treatments of captan and benomyl are estimated to provide control of most summer diseases such that there would be no significant economic impacts. The exception would be for brown rot where growers would need to rely on thiram, sulfur or ferbam.

Based on current chemical costs, estimated costs to treat an apple orchard with captan instead of EBDC fungicides result in an estimated cost savings of $14.49 to $16.02 per acre or approximately $4.7 million savings. However, captan is less effective than EBDCs in controlling apple rust and scab fungi and estimated losses up to nine percent may occur on acres affected by apple rust. Agency calculations result in an estimated reduced production of up to nine percent on the affected acres or for the overall U.S. reduced production of apples by 0.5 to 1.8 percent (approximately a loss of $5 to $17 million). Considering the savings from using less expensive fungicides and the possible reduced yields that could result from use of these fungicides, cancellation of EBDC fungicides could result in net producer losses of $0.3 million to $10.3 million (Table III-2).

j. Peaches and nectarines

Although maneb is registered for use to control peach leaf curl, scab, shothole (Coryneum blight) and brown rot or blossom blight, its use on peaches and nectarines is limited. Brown rot is one of the most important diseases of peaches and nectarines as it can attack blossoms, flowers, twigs and fruit. Peach leaf curl is especially important in California orchards.

There are registered chemical alternatives to treat all four of the peach and nectarine pathogens for which maneb is registered. These include captan, chlorothalonil, benomyl, dichloran, copper fungicides and several sterol inhibiting fungicides. Comparative efficacy trials reported in the American Phytopathological Society's Fungicide and Nematicide Test Results indicate that benomyl and thiophanate-methyl are the most effective fungicides at controlling brown rot. However, EBDCs would provide a role as one of the available fungicides which can slow or inhibit the development of fungal resistance to benomyl and thiophanate-methyl. EBDC fungicides are infrequently recommended by State authorities and generally are not considered the product of choice by State experts. EBDC fungicides are applied to less than three percent of the U.S. acreage most of this usage is for western peach orchards (USEPA, 1988m).

The Agency has estimated that chlorothalonil likely would replace EBDC fungicides if these registrations were cancelled. If chlorothalonil totally replaced EBDCs, based on the current chemical costs, the annual treatment cost per affected acre is estimated to increase from $10.60 per acre treatment of EBDC to $13.93 per acre treatment of chlorothalonil which results in a projected production cost increase of $3.33 per acre. Total cost increases are estimated to be negligible, less than $14,000, and no yield effects are expected (Table III-2).

k. Cranberries

In 1987, about 3.3 million barrels of cranberries were produced in the U.S. with a farm gate value of over $170 million. Massachusetts and Wisconsin are the two major producing states accounting for nearly 80 percent of domestic production. In 1988, approximately 15 percent of the cranberry crop was treated with EBDC fungicides.

EBDC fungicides are used to control fruit rot and twig rot (primarily in Pacific Northwest). Chlorothalonil is an economic alternative to EBDC fungicides and is used more widely than EBDCs. If EBDCs are cancelled, fungicide cost would increase by about $100,000 per year for the entire industry. This increase would be negligible.

1. Grapes

Domestic grape production is highly concentrated in a few states. Ninety-nine percent of the grapes are produced in California, Washington, New York, Michigan, and Pennsylvania. California alone accounts for approximately 90 percent of the grape production each year. California growers produce several varieties of grapes that are used to make wine, dried for raisin production or consumed on a fresh basis. Growers in the other four major grape-producing states raise few varieties (primarily Concord grapes) which are crushed for juice, jam and concentrate. A small quantity of the crush is used for wine production (USEPA, 1988h).

Mancozeb and maneb are registered to control five fungal diseases of grape. Table III-6 is a matrix of the disease control claims for each of the registered EBDC fungicides. Black rot and downy mildew are most important in the eastern U.S.; Botrytis is important in all grape growing areas; and Phomopsis cane and leaf spot (or blight) continually has been more important in California and in the Northeast.

Maneb and mancozeb are widely recommended by State authorities for control of plant diseases on grapes. Approximately 300,000 pounds ai of EBDC fungicides are applied each year to U.S. vineyards representing about 22 percent of the total grape acreage (USEPA, 1988h).

Table III-6

Summary of EBDC Fungicides Registered to Control Diseases of Grapes

Fungal Disease	Mancozeb	Maneb
Black rot	x	x
Botrytis bunch rot	x	x
Downy mildew	x	
Phomopsis cane blight	x	

Use of resistant varieties can reduce the need for fungicides. However, because of the long lived nature of a grape vineyard and consumer demand for certain wine and raisin varieties, growers continue to produce the varieties of high demand.

Alternative fungicides are available for all of these fungal diseases. Captan, benomyl, iprodione, triadimefon, ferbam, copper fungicides and dichloran are registered for control of one or more of the five diseases of concern. Although comparative product performance data statistically evaluating grape yield differences between EBDC fungicides and alternatives are not available, the major benefits from EBDC fungicides appear to be the multi-site mode of action of these fungicides which helps reduce the build-up of fungicide resistance and lower production costs by using the relatively inexpensive EBDCs. It should be noted that captan and sodium arsenite in California only, are the only alternatives to mancozeb for Phomopsis cane and leaf spot.

Production costs may be reduced by $0.36 per acre if growers switch to captan or increased by as much as $10.95 per acre if growers switch to benomyl (USEPA, 1988h). Experts from grape producing states indicated that if EBDC registrations are cancelled most of the economic impacts to grapes would occur in the East and Midwest due to possible yield losses from black rot (2 to 5 percent) and downy mildew (0 to 5 percent) (USEPA, 1988h). EPA estimated that overall yield losses would not exceed five percent. These two diseases are not important in grape growing areas of the west. In aggregate for the total U.S., the value of the grape crop is projected to be reduced by an estimated $1 to $3 million (Table III-2).

m. Bananas

If EBDC registrations in the U.S. were cancelled, all EBDC food tolerances would be cancelled and food imported into the U.S. could be seized if contaminated with EBDCs. This analysis is not intended to consider the economic impacts of the proposed decision on foreign countries, but does consider any possible economic impacts the proposed decision would have on U.S. consumers of bananas, either in reduced availability, reduced quality or increased price.

Bananas are the single most popular fresh fruit consumed in the U.S. Commercial banana production in the U.S. is restricted almost exclusively to Hawaii with virtually all Hawaiian bananas consumed locally. Essentially all bananas consumed on mainland U.S. are imported. The major supply countries are: Colombia, Costa Rica, Ecuador, Guatemala, Honduras, and Panama. The U.S. imported 3,243 thousand tons of bananas in 1986 with an estimated value at just over $700 million.

Maneb and mancozeb are registered for use on bananas to control Sigatoka disease and tolerances have been established that apply to both imported and domestic (Hawaiian) bananas. Actual quantitative usage of banana fungicides is difficult to determine. Due to the small amount of acreage in Hawaii (approximately 1,000 acres), fungicide usage on Hawaiian bananas is not reported. In addition, there is limited information available on usage estimates for Latin America. A maximum of 53,000 pounds ai of mancozeb is estimated to be applied to Hawaiian banana acreage each year. International usage of mancozeb on bananas is estimated at nine to eleven million pounds ai annually. Nearly all banana acreage outside the U.S. is treated with EBDCs because of the importance of Sigatoka disease to banana production (USEPA, 1988b).

If EBDC registrations were cancelled, banana growers likely would substitute propiconazole or tridemorph with petroleum oil. The use of these alternatives could increase annual treatment cost by $300 to $400 per acre or $300,000 to $400,000 in total. Minor market and consumer impacts are anticipated.

Banana producing countries are the largest banana consuming countries. Also, the U.S. consumes about five percent of the world banana production. The Agency believes it is possible that any reduced quality bananas or shortages in supply would be absorbed by the local economies of the exporting country in order to maintain a constant supply of high quality product to the international market. Such a policy would insure market share and a continued steady supply of needed currency. However, if exporting counties do not absorb the reduced quality and shortages in supply, consumer prices in the U.S. may increase.

n. Sweet corn

Sweet corn is widely grown in the U.S. with production for fresh market sale in the summer occurring in nearly all states. Production for national sale during the fall, winter and spring occurs in Florida, Texas and California with only a small percentage of the production in Texas and California. About a half dozen northern states grow sweet corn for processing.

Maneb and mancozeb are registered to control northern and southern corn leaf blight on sweet corn; metiram is registered for use only in Florida. In addition, mancozeb is registered to control another foliar fungal disease called common rust. Northern and southern corn leaf blight tend to be more important in the southern States and common rust tends to occur more in the north central States (USEPA, 1988q).

The use of resistant or tolerant varieties is considered by most State authorities to be the best control measure for these three diseases. There is general resistance to rust in field corn hybrids and some sweet corn hybrids, but many commercial sweet corn hybrids are susceptible to rust, especially the new high sugar hybrids preferred for fresh market and by some processors.

The only registered alternative to the EBDC fungicides for control of these three diseases is chlorothalonil and according to the chlorothalonil label, it can only be used on sweet corn grown for fresh market, not sweet corn grown for processing. In addition, certain resistant prone fungicides show promise for control of these pathogens particularly propiconazole for which registration currently is being pursued. According to experts contacted by the EPA, use of fungicides is only economical when disease pressure is moderate to severe and when the fungi invade young plants (USEPA, 1988q).

Ten field studies on the comparative control of northern and southern leaf blight were reviewed. No yield data were available, but a statistical analysis of efficacy data indicated no significant differences between chlorothalonil and the EBDCs. Similarly, nine field studies on the comparative control of rust were reviewed. Mancozeb provided statistically significant disease reduction over chlorothalonil in only one trail. Considering the above information, the Agency concluded that if the EBDC fungicides were no longer available, yields of sweet corn grown for fresh market sale should not be affected, but based on current chemical costs, costs for disease control would rise. The cost per application per acre is projected to increase by $0.75 if chlorothalonil was substituted for EBDCs resulting in a yearly cost increase of $405,000 on sweet corn grown in

Florida. Because chlorothalonil is not registered for use on sweet corn that is to be processed, production costs on sweet corn grown in the Midwest for processing would fall because growers would not be applying fungicides. However, yields on affected acres are estimated to decline due to the impacts of the diseases on cob size, number of ears per plant, and kernel size. It is estimated that using currently available sweet corn hybrids (including resistant strains) in two or three years out of five a 10 percent yield loss could occur and in one year out of five a 30 percent yield loss could occur on 50,000 acres or more. The value of the possible range of crop loss has been estimated at between $1.7 and 2.1 million (USEPA, 1988q).

Impacts on consumers are estimated to include probable price increases for canned and frozen sweet corn in years with yield losses (Table III-2).

o. Small grains

In this country, most of the small grains are grown in drier regions of the country where fungicide usage is not particularly beneficial to yield. Currently, in excess of 95 percent of the domestic wheat, barley, oats and rye acreage is not treated with fungicides. Average or most likely estimates of annual usage indicates that 330,000 acres of wheat, 60,000 acres of barley and 15,000 acres of oats and rye are treated with mancozeb (USEPA, 1988o). There is no information indicating actual use on rye, but some use is possible.

Mancozeb is registered for control of Helminthosporium leaf spot, leaf rust, Septoria leaf spot, Septoria glume blotch and tan spot on wheat, barley, oats and rye. Propiconazole is registered for control of the leaf spots and rust diseases on wheat, barley and rye (not oats); triadimefon is registered for control of leaf spots and rust diseases on wheat and barley; and copper hydroxide is registered for control of leaf spots of wheat and barley. Fungicides are recommended to be used as part of a comprehensive disease management program which includes cultural controls as well as estimating yield loss, crop prices and production cost before applying any fungicide. Therefore, the Agency believes that fungicides typically are only used on grain fields with high yields and that are under irrigation.

Triadimefon and propiconazole are the most likely used substitutes for EBDC fungicides although they currently are more expensive than EBDCs. There is not enough information available to determine the magnitude, if any, of possible yield impacts from loss of EBDCs on small grains. However, EPA has determined that overall bounds could range from zero yield loss and cost of production changes to a value of 30 percent crop loss on the treated acres if no fungicides were available or if fungal pathogens became resistant to alternative fungicides. More likely yield losses are estimated by EPA to be 7.5 to 15 percent on affected acres.

If EBDC registrations are cancelled, it is estimated that users of EBDCs could have losses of about $2.0 million attributed to projected increased costs of disease control with no yield loss, about $4.6 million with a 7.5 percent yield loss, $7.2 million with a 15 percent yield loss and about $12.3 million if yield losses were 30 percent on all treated acres. The four small grain crops combined have a market value of about $6.6 billion so the worst case loss is estimated to be about 0.2 percent of the combined values of these crops. Under the worst case, with a 30 percent yield loss, farmers who used EBDCs are estimated to have a reduction of about 30 percent of gross revenues per acre, which could result in negative net returns. Growers with such high yield losses would need to make changes in practices or crops produced to reduce the magnitude of losses. In most cases, only farmers with yield losses of under eight percent would have positive net returns. However, growers with yield losses in this range still may find it more profitable to shift out of wheat or barley. Oat producers who used EBDCs potentially would have more serious problems since this crop usually is less profitable than wheat or barley and there are no registered alternatives for oats. Rye is also a less profitable crop than wheat or barley and, although there are registered alternatives to EBDCs on rye, growers of rye could have similar problems as those faced by growers of oats. However, use of EBDCs on oats and rye is extremely limited and only a few growers would suffer any impacts.

Loss of EBDCs could result in gains to non-users if the price per bushel of grain were to rise due to a loss of crop yield nationwide, should yield be so impacted. The high estimate of the increased cost on a per bushel basis would result in possible gains of up to $90 million which represents up to about one percent of the crop value. However, it is expected that price increases would result in relatively small increases in the price of small grain products.

p. Other crops

Information is not available to enable the Agency to conduct a quantitative benefits analysis for all crops, especially those where a small percentage of the crop is believed to be treated. [4] As stated in the introduction to this chapter, the Agency encourages submission of factual data describing any benefits that may be gained from the use of EBDC or other fungicides or other methods of control on any crops, especially usage and comparative product performance data for minor crops. For crops marked by an asterisk in Table III-1, the Agency knows of no use of EBDC's and therefore it assumes there are no benefits on these sites. Benefits estimates for lima beans and green beans given in Chapter IV (Table IV-2) were based on an update of the 1978 USDA/States/EPA Assessment of EBDC Fungicides Used in Agriculture.

---

[4] Crops where the Agency had insufficient data to conduct a quantitative benefits assessment include: almonds, apricots, asparagus, casaba melons, crabapples/quince, crenshaw melons, eggplant, endive, fennel, fig, kohlrabi, papaya, pecans, pears, peas, pineapples, and rhubarb.

4. Seed treatments

Mancozeb and maneb are registered for use as a seed treatment on a variety of crop plants, but the Agency is aware of use only on small grains (DPRA, 1988c). EBDC seed treatments are used on small grains in a wide geographic dispersion on eight to ten percent of the crop. Approximately 830,000 pounds ai of EBDC are used annually on barley, oats, rye and wheat to help control smuts, bunt, damping-off, and seedling blights (DPRA, 1988c). The major alternatives are captan, carboxin, thiram and triadimenol. Field trial data and the opinion of plant pathologists lead the Agency to conclude that a combination of carboxin and thiram generally is more effective than EBDC fungicides (DPRA, 1988c). EBDC fungicides are often preferred to captan because the latter does not control the smut and bunt fungi. Cancellation of EBDC seed treatment uses is estimated to result in a net aggregate cost increase of $7.4 million because of the currently higher costs of the carboxin and thiram combination.

5. Non-food crops

a. Ornamental plants

For this analysis, the term ornamental plants includes shade trees, landscape woody shrubs and herbaceous perennials, ornamental conifers, floriculture crops, foliage crops and bedding plants. Mancozeb and maneb are registered for use on one or more of these plant groupings which represent over 70 plant species. The EPA estimates that about 150,000 pounds ai of

EBDC's are used on ornamental plants. This represents 15 to 20 percent of fungicide usage on ornamentals. Benomyl, chlorothalonil, dichloran (DCNA), fenarimol, iprodione, thiophanate-methyl, triadimefon, triforine, vinclozolin and other fungicides are registered for use on ornamental crop plants. However, most of these fungicides are not registered for most ornamental plants. In fact, because the ornamentals share of the fungicide market is small, there are only a few registered materials for most plants and there are no registered alternatives to EBDCs for many diseases of ornamental plants. EBDC fungicides are recommended by many ornamental plant disease specialists. Many ornamental plant diseases are not listed on the pesticide labels, but specialists recommend using EBDC fungicides to control such diseases if the crop plant is listed on the label. Labels for benomyl also are quite broad, but iprodione, fenarimol, triadimefon, triforine and vinclozolin labels list only a few ornamentals, usually the higher production crops such as roses, carnations and chrysanthemums. The broad label increases the value of EBDC fungicides for these crops; benomyl's usefulness is limited by potential or actual fungal resistance.

Quality is often equated with yield in the ornamental industry. The Agency believes that alternatives to EBDCs usually control a slightly different or, more often, a smaller spectrum of fungal pathogens than alternative fungicides. Also, fungicidal resistance, especially to benzimidazole fungicides, limits the availability of effective alternatives. EBDCs, with their broad spectrum of activity, control many types of fungi, and are valuable to the ornamental industry. Therefore, there are not fungicides available which are complete replacements for the EBDCs in the ornamental industry. If growers were to shift all EBDC usage to chlorothalonil, due to current differences in chemical costs, treatment costs would increase by approximately $450,000 per year. Although the Agency does not have quantitative data to estimate impacts, it believes that some yield and quality losses would be likely because chlorothalonil in addition to other alternative fungicides are not perfect substitutes for EBDCs and are not registered for the wide spectrum of ornamental plants. Therefore, benefits could be significantly higher for this commodity group than the projected increased treatment costs alone.

b. Turfgrass

Mancozeb and maneb also are registered to control fungal pathogens of turfgrass. For homeowners and also for persons growing lawns and turfgrass for non-commercial purposes, judicious management may result in grass-covered areas which may grow satisfactorily for years without the application of any fungicides. For the commercial operator, however, such as one managing a golf course, who requires a "first rate" appearance of the turfgrass throughout the year, fungicide use may be essential and necessary, particularly during certain seasons. It is desirable for such an operator to have a wide range of turfgrass fungicides available for use. The use of numerous fungicides provides the option of continually rotating between several fungicides which can adequately control the various disease problems. Such a rotation helps prevent the development of fungicide resistance, but the Agency does not have the data necessary to quantify the potential loss if resistance were to develop following cancellation of EBDC registrations.

Mancozeb is more frequently used and considered a more valuable fungicide to turfgrass managers than maneb. Mancozeb is registered to control 11 of the 27 turfgrass pathogens and has multi-site mode of action. Consequently, it is used in rotation with or tank-mixed with benzimidazole fungicides and single-site type fungicides.

EPA has estimated that cancellation of EBDC fungicide registrations potentially would increase the cost of golf course maintenance because EBDC fungicides currently are less expensive than chlorothalonil by approximately $10 per acre or just over $2,000 per golf course. Because usage of EBDCs is low, the overall impacts are expected to be minimal, approximately $14,000 on a nationwide basis. However, over 50 percent of the golf courses surveyed by the EPA reported resistance to benomyl and the use of multi-site mode of action alternatives such as EBDCs and chlorothalonil may be needed to control turfgrass problems on these golf courses in the future (USEPA, 1988s).

6. Industrial sites

a. Paper mills

The largest industrial user of process water is the paper industry. The process water needs biocides to prevent the growth of filamentous fungi, spore and non-spore forming bacteria, yeasts and other microorganisms which produce slime that can clog pipes, screens and filters resulting in spots or breaks in the roll of paper.

Biocides to control slime forming microorganisms are usually introduced early in the paper making process either on a continuous-feed basis or by slug feeding. Those paper mills that use nabam reportedly use a 50:50 combination product of nabam and dibam; about 250,000 pounds ai of nabam are used annually (DPRA, 1988d). The predominant biocides are MBT (methylenebisthiocyanate), DMTT (tetrahyro-3,5-dimethyl-2H-1,3,5-thiadiazine-2-thione) and isothiazolone while nabam/dibam products are used infrequently along with quaternary ammonium compounds and DBNPA (2,2-dibromo-3-nitrilopropionamide). About four percent of the paper produced using biocides in U.S. comes from mills using nabam/dibam.

The biocide of choice at a particular mill is largely dependent on factors unique to that mill. These factors include the pH of the process water, temperature of the system, and type of paper being produced, among others. Because biocides do not perform equivalently in any given system, relative cost comparisons were made based on average product prices and treatment rates for the most common conditions.

If nabam uses were cancelled, it is assumed that one-half of the nabam/dibam treatments would be replaced with MBT and one-half with isothiazolone. The reason for splitting the nabam tonnage between the two biocides is to cover the total pH range at which nabam/dibam is effective. If nabam were cancelled, the Agency estimates that the cost to the paper industry for biocides would decline by $700,000 or less than two percent of the industry costs for biocides. Therefore, the overall production costs would decrease for those paper mills currently using nabam. This outcome is based upon the assumption that there is not a decline in the efficacy of controlling slime-forming microorganisms through use of alternative control methods.

b. Water cooling systems

The major types of equipment associated with cooling water systems are cooling towers and air washers, with the former being by far more prevalent both in terms of numbers and use of biocides. The function of a cooling tower is to allow the maximum loss of waste heat from recirculating waters to the atmosphere. This waste heat can be from industrial or institutional applications. Microorganisms grow well in the warm, well oxygenated environment of cooling towers. The slime produced by the microorganisms can clog the heat transfer system reducing water flow and cooling ability as well as causing corrosion and pitting of metal surfaces. Air washer systems control humidity and temperature as well as remove airborne particulates, aerosols and odors. Air washer systems that are used primarily for climate control require a minimum of biocides, but those that remove particulates require biocides. Most cooling water experts agree that there are adequate replacements for nabam (DPRA, 1988d). Smaller companies servicing water cooling systems may have fewer alternatives available than will larger companies because smaller companies may not have the capital to keep a wide range of products on hand or have the facilities to store a large number of products. DBNPA, MBT and isothiazolone are the most likely alternatives. Depending on the alternative chosen, it is estimated that there would be no increase in costs to an increase of $2.64 per 1000 gallons of treated water. The high end of this range represents approximately a 170 percent increase. Water cooling service companies would probably choose the least expensive alternatives which would be either DBNPA or MBT and the impacts of nabam cancellation are estimated to be minimal (DPRA, 1988d).

c. Sugar mills

Both cane and sugar beet mills use biocides, although the type of mills used in Hawaii do not use nabam (DPRA, 1988d). Both cane and beet operations use biocides to prevent the growth of bacteria which interfere with sugar processing. Nabam/dibam, Busan^{TM} (a combination of disodium cyanodithioimidocarbonate and potassium n-methyldithiocarbamate), and DBNPA are registered for use in sugar mills. Other biocide materials include formaldehyde and chlorine dioxide which are listed by the FDA in the group of chemicals that are generally regarded as safe under Title 21, Chapter 1, Part 182. However, use of formaldehyde and chlorine dioxide has reduced over the last few years. A few sugar mills use heat sterilization as an alternative to chemical biocides. The nabam/dibam combination is the most frequently used biocide in sugar mills, using approximately 165,000 to 200,000 pounds of ai a year. Approximately 50 to 60 percent of all mills use nabam/dibam as a biocide (DPRA, 1988d). Use of DBNPA is limited because registration labels state that by-products from mills using DBNPA cannot be used as animal feed.

Nabam/dibam is the lowest cost treatment, followed by Busan and then formaldehyde (DPRA, 1988d). Formaldehyde is considered the most effective compound and is often used as a rescue compound if less expensive materials fail. However, as formaldehyde costs are high, Busan is assumed to be the only remaining viable choice. Substitution of Busan for nabam/dibam is estimated to result in an aggregate increased production cost of $409,200 to $496,900 which would represent less than a 0.02 percent increase relative to the aggregate value of sugar and sugar processing by-products. The increased costs is due to the larger amount of ai needed for Busan treatment compared to nabam/dibam.

d. Oil well drilling fluids

Nabam is registered for use in three oil well fluid applications: drilling, secondary/tertiary recovery and fracturing. The biocides used in oil well fluids are typically provided by oil well service companies who determine which chemicals or combination of chemicals are best in each situation.

Alternatives include acrolein, which is only used in secondary oil recovery systems; DBNPA, which is used in fracturing; formaldehyde/paraformaldehyde, which was once among the most widely used, but whose use has declined recently; glutaraldehyde, used in all three oil well fluid applications; isothiazolone, whose usage is growing rapidly, but may not work well in secondary oil recovery systems; quaternary ammonium compounds, which are used only in secondary oil recovery systems; and triazine, which is used primarily in fracturing (DPRA, 1988d). Nabam's effectiveness is unclear. Some experts feel it is very effective, while others feel that it does not perform as well as alternative biocides and will use nabam only at a client's request. For oil well fluid use, there is at least one alternative that costs less to use than nabam/dibam. This fact, combined with the fact that nabam/dibam has such a small percentage (less than five percent) of biocide sales in oil well fluids, implies that aggregate impacts should be minimal.

e. Metal working coolant

Based on available usage estimates, the Agency believes that nabam is not currently used as an additive for metal working coolants; therefore, the Agency would assume it has no benefits at this site. An alternative chemical, methylene bisthiocyanate, is being used (DPRA, 1988d).

B. ANALYSIS OF REBUTTAL COMMENTS

Rebuttal comments submitted to the Agency in response to the Initiation of Special Review (PD 1) issued in July, 1987 were reviewed and the Agency's responses are provided below. Rebuttal comments are on file in the EBDC Public Docket.

Testimonial Comments

In response to the EBDC PD 1, the Agency received approximately 100 responses pertaining to the benefits of EBDC fungicides. Most of these comments were undocumented testimonials. Generally, these comments claimed the usefulness of the EBDCs in controlling diseases on a wide variety of agricultural crops, cost effectiveness of EBDC fungicides as compared to alternatives and potential for yield and quality reduction on many crops if the EBDC registrations were cancelled.

These comments also noted that there has been little or no significant resistance problems with the EBDCs and that they have been used in conjunction with fungicides to which fungal resistance has developed or have the potential for resistance development.

The Agency did not receive any testimonial benefits comments on non-agricultural uses of the EBDCs.

Rebuttal Comment

Pennwalt Chemical Corporation submitted a two-part response to the PD 1. The first submission contained estimates of usage, efficacy, comparative performance and market parameters and used to develop estimates of changes in benefits under varying regulatory scenarios. The second submission was an analysis of economic welfare impacts of a maneb cancellation.

Agency Response

The Agency used the first submission to refine the Agency's benefit estimates. The Agency agrees with the approach used in the second Pennwalt submission to assess the economic impact of cancellation of these EBDC products. However, the analysis was dependant on the input data and assumptions made about the effect that maneb and alternative pesticides have on the production of a given commodity. The specific data that are used to reflect the market characterization also are crucial (Arnold, 1988; Frohberg, 1988; Malik et al, 1988). The Agency concludes that the submission relied on comparative efficacy and product performance assumptions that were not well documented, as well as estimates of supply and transmission elasticities that do not appear to be plausible. Therefore, the specific quantitative results cannot be accepted as correct on their face value.

Rebuttal Comment

Rohm and Haas Company submitted comments which detailed estimates of pesticide usage patterns for mancozeb and alternative fungicides on certain crops, cost comparisons on a per pound/per acre treatment and per season/per acre basis, comparative yield and quality effects and economic effects.

Agency Response

This information has been incorporated into the Agency's own site-by-site benefit analysis. The submitted information supports Agency conclusions that mancozeb uses have alternatives for some but not all uses, and that in some cases substitutions may involve higher costs and/or reduced yields.

Rebuttal Comment

The BASF and FMC Corporations submitted information on fungicide usage patterns, the properties of metiram and its alternatives with respect to diseases controlled, descriptions of major diseases and their effects, crop production statistics, State recommendation summaries and relative product performance of metiram and alternative fungicides for apples and potatoes.

Agency Response

This submission generally summarized information already available to the Agency and has been used in the benefit assessment.

Rebuttal Comment

Alco Chemical Corporation and Vinings Industries submitted benefits information on nabam containing microbiocides for microorganism control in cooling water systems, pulp and paper mills, cane and beet sugar mills and petroleum recovery operations. They concluded that for cooling water systems, pulp/paper mills and cane/sugar beet mills, nabam products are more cost-effective (dollars per treated volume of protected material) than were alternative chemicals. For petroleum recovery operations, they found alternative chemicals to be more cost-effective on a comparative basis.

Agency Response

The Agency's analysis found that on all sites analyzed, alternatives to nabam were more cost-effective. These differences can be accounted for by different assumptions on likely treatment rates, probable alternative chemicals used and the use of wholesale product prices (Alco and Vinings) as opposed to end-user cost estimates.

IV. RISK/BENEFIT ANALYSIS AND REGULATORY OPTIONS

A. INTRODUCTION

FIFRA requires the Agency to weigh the risks against the benefits for each use of a pesticide in order to determine whether continued registration would cause unreasonable adverse effects on the environment. In Chapters II and III, the Agency discussed the risks posed by exposure to the EBDCs and the benefits estimated to be derived from their registered uses. To determine whether continued registration of the EBDCs is appropriate, the Agency has identified a number of regulatory options, and has evaluated each option for its impacts on both risks and benefits.

In addition, the Agency has identified registered alternative pesticides for most uses of the EBDCs. The general risks of the alternative pesticides have been summarized based on available data (See Table IV-1).

This section identifies the regulatory options available to the Agency to reduce the risks from the registered uses of the EBDCs. In conducting its analysis, the Agency considered the aggregate risks posed by the EBDCs and ETU, the extent to which registered uses are being supported by registrants and, where appropriate, the risks and benefits of individual uses.

B. RISK CONCLUSIONS

Exposure to the EBDCs and ETU can occur through application of the pesticides to food crops and eating foods containing residues of EBDCs and ETU. Exposure to EBDCs and ETU can also occur from application to non-food crops and from industrial application of these pesticides. The entire U.S. population may be exposed to EBDC and ETU residues from food, non-food and industrial uses. These exposures and estimated associated risks are discussed in Sections II.B (2) and (3) of this document.

1. Carcinogenicity

As discussed in the PD 1 and in Section II.A (1) of this document, the Agency does not have adequate carcinogenicity studies for any of the individual EBDCs. Long-term animal studies (rat and mouse) have been required for each of the EBDCs through Registration Standards and/or Data Call-Ins. The Agency has several positive long-term animal carcinogenicity studies for the EBDC contaminant, degradate and metabolite, ETU. Based upon the data from these studies, the Agency has concluded that ETU meets the criteria of a Group B_2 carcinogen (probable human carcinogen). ETU induced an increased incidence of thyroid follicular cell adenomas and adenocarcinomas in Fisher 344 (NTP, 1989) and Charles River CD rats (Ulland, 1972 and Graham, 1975) and an increase of hepatomas in three strains of mice (Innes, 1969 and NTP, 1989). Using data from a portion of the NTP mouse study, the Agency calculated a preliminary new Q_1^* (potency factor). This carcinogen potency factor was derived from a linearized multistage risk model and the estimates of exposure were then used to estimate the 95th percentile upper bound, lifetime probability of excess carcinogenic risk to humans. The EBDCs and ETU have been tested for mutagenicity in several assay systems. Results of the available studies were both positive and negative. Evidence of mutagenicity from these studies provided supportive evidence of the carcinogenic effect. The specific risk estimates for carcinogenicity were presented in Sections II.B (3)(a)(1), (b)(1), and (c)(1) of this document and include both dietary risks and mixer/loader/applicator risks from food, non-food and industrial uses of the EBDCs.

2. Developmental Toxicity

Section II.A(2) presented the Agency's concerns regarding developmental/fetotoxic effects of ETU and the EBDCs. Available data (Khera, 1973) demonstrate ETU's potential to cause these effects in rats. The NOAEL (No-Observable-Adverse-Effect Level) is equal to or less than 5 mg/kg/day. Mancozeb has also been shown to be developmentally toxic in rats. The NOEL is 128 mg/kg/day. Additionally, rabbits dosed with Aquatreat DN-30 (a formulated product containing 30% nabam) showed developmental effects at the low dose tested of 3.0 mg/kg/day.

3. Thyroid Effects

Section II.A (3) presented information on thyroid effects of ETU and the EBDCs. Studies with ETU and mancozeb have demonstrated effects in rats and mice (thyroid hyperplasia). The LEL (Lowest-Observable-Effect Level) from the two year rat study is less than 5 ppm of ETU.

4. Risks from Alternatives

The chemical alternatives to the EBDCs are listed in Table IV-1 of this chapter along with characterization of the available information on their carcinogenicity, mutagenicity, and

Table IV-1

Toxicity and Status of Major Alternatives to the EBDCs

FUNGICIDE	TOXICITY/[a] CARCINO	MUTA	REPRO	TERAT	STATUS/[b]
Anilazine (Dyrene)	-	•	•	•	RS 12/83
Triadimefon (Bayleton)	?	-	-	+	No RS;
Benomyl (Benlate)	qC	+	+	+	SR 82; SRR 87
Captan	B_2	•	•	•	SR; 2/89
Coppers	2	2	2	2	RS 86
Chlorothalonil	B_2	•	•	-	SRR 9/88
Dichloran	•	+/•^{4}	-	-	RS 83
Dodine	•	•	?	•	RS 88
Ferbam		No RS			
Iprodione	-	+/-^{3} ?		-	
Metalaxyl (Ridomil)	E	-	-	-	SRR 3/88
Propiconazole (Tilt)	qC/D^1	-	-	-	
Sulfur	•	•	•	•	RS 1/83
Thiram	•	-	•	•	RS 7/84

---

[a] + = positive finding
- = negative finding

• = no data or additional data required
? = don't know, e.g. dose not high enough, or regulatory decision made not to ask for more data

[b] RS = Registration Standard
SR = Special Review

SRR = Second Round Review in the Registration Standard Process
B_2 = Probable human carcinogen
C = Possible human carcinogen
qC = Possible human carcinogen; risk should be quantified
D = Not classifiable as to human carcinogenicity
E = Evidence of non-carcinogenicity for humans

1 = OPP Peer Review said (q) quantifiable C; the SAP said it was a D.

2 = Data "not available" and required only for MP's used to formulate products for indoor use only (Ref. RS Copper Sulfate 1986; RS Group II Copper Compounds 1987).

3 = only one study was (+); but five were (-).

4 = one or more studies were +; there is no additional data being requested.

reproductive and developmental effects. For several of these chemicals, the data base is incomplete which makes it difficult to judge the relative toxicity of the alternatives as compared to the EBDCs. Missing data will be obtained for these chemicals through the Agency's reregistration process.

The major alternatives to the EBDCs (excluding nabam) are captan and chlorothalonil. Benomyl is also used on many of the same sites. Captan and chlorothalonil are Group B_2 carcinogens and benomyl is a Group C(q) carcinogen (Table IV-1). The Agency has recently completed a Final Determination PD 4 for captan and found it not to cause developmental, mutagenic or reproductive risks of concern at this time. Risks from dietary exposure from captan are estimated at 10^{-6}. Chlorothalonil was recently evaluated through EPA's reregistration process. Carcinogenic dietary risks are estimated to be 10^{-6} from chlorothalonil and 10^{-6} from its contaminant hexachlorobenzene (HCB), which is also a B_2 carcinogen. It was determined that the risks from chlorothalonil and HCB did not meet the criteria for initiating a Special Review at that time. In July, 1987, the Agency issued a Registration Standard for benomyl. Although it was found to be a carcinogen, and a developmental and reproductive toxicant, the Agency at that time determined those risks to be acceptable. Since that time, the Agency has reconsidered the carcinogenicity classification of benomyl and has concluded that, in addition to remaining a possible human (Group C), carcinogen, its carcinogenic risks should be quantified. The Agency is currently quantifying those risks. If the risk estimates indicate a potential risk of concern, the Agency will consider further regulatory action.

As part of the Agency's comparative risk/benefit assessment of major fungicides, dietary risks for the five EBDC chemicals, captan and chlorothalonil were compared based on hypothetical cancellation scenarios. Even though benomyl's risks are now being quantified, it would not be appropriate to consider benomyl an alternative to the EBDCs, captan, or chlorothalonil, because benomyl tends to be used with each of the other three fungicides, rather than in lieu of them, due to benomyl resistance problems. (See Fungicide Review Strategy for Captan, Chlorothalonil and the EBDCs, 1988.) The Agency estimated potential shifts in usage and dietary risks if one or more of the three fungicides (captan, chlorothalonil and the EBDCs) were cancelled. No cancellation scenario caused greater than one-half an order of magnitude risk increase to any of the three fungicides. It was concluded that cancellation of one or two of the three fungicides would not cause a significant difference in the risk/benefit conclusion for the remaining fungicide(s).

C. BENEFIT CONCLUSIONS

Based on available data, the benefits of the EBDCs were assessed for all viable regulatory options including the cancellation of some or all registered uses of EBDC fungicides and other measures to reduce the risks from EBDCs. As explained in Section III of this document, if the EBDC registrations on all food crops were cancelled, estimated direct losses to growers (producer impacts) would be approximately $46 to $75 million and projected loss to society, or efficiency impacts, at least in the short term, would range from approximately $90 to $305 million. Efficiency impacts are concentrated on three crops: lettuce, peppers, and celery. A major portion of the projected yield loss impact would be on apples, onions, wheat, and spinach because of the lack of viable registered alternatives for these crops. Over the long term, impacts in yield and consumer prices could be reduced if more acreage were planted to compensate for the losses, more effective alternatives were registered, non-chemical alternatives were developed, etc.

Registered alternatives exist for almost all uses of the EBDCs, but in most cases the alternatives are more expensive. However, for some food crops, projected increased production costs are offset by estimated increases in yields.

The estimated impact of cancellation on non-food uses is $5 to $15 million of producer/user impacts, chiefly for commercial ornamentals. For certain industrial sites, nabam is more expensive to use than certain alternatives and costs to industrial users could decrease with a shift to alternative biocides.

D. DEVELOPMENT OF REGULATORY OPTIONS

There are four basic options for regulating all pesticides:

Option 1 - Continuation of Registration Without Changes

Option 2 - Continuation of Registration with Modifications to the Terms and Conditions of Registration

Option 3 - Partial Cancellation

Option 4 - Cancellation of All Registrations

Option 1, Continuation of Registration without Change and Option 4, Cancellation of All Registrations, are at opposite ends of the risk/benefit spectrum. Adoption of Option 1 would be appropriate when the Agency has concluded that the level of risk is acceptable in light of the pesticide's benefits and that further risk reduction measures are not necessary to assure that the use of the pesticide meets the standard for continued registration. Adoption of Options 3 or 4, Partial or Total Cancellation, would be appropriate when the Agency has concluded that the risks outweigh the benefits, and that these risks cannot be mitigated to an acceptable level, in light of the benefits, by any other measure short of cancellation. Cancellation may affect all uses of a compound, only specific uses or specific formulations, or specific application methods. Option 2 is appropriate when the risks of a pesticide use can be reduced to a level where the benefits of use outweigh the risks. This risk reduction is accomplished by modifying the terms and conditions of the pesticide's registration. These modifications, which are expressed through the pesticide's labeling, are, for the most part, changes in the way the pesticide is used or the amount of the pesticide that may be used. These changes are designed to reduce exposure to the pesticide and thereby reduce or eliminate the risk from the pesticide. Risk reduction measures were considered and evaluated for their potential effectiveness and feasibility.

1. Measures to Reduce Dietary Exposure

Amounts of pesticide residues on food crops are affected by such factors as quantity of active ingredient used, the solvents used for dilution, mode and schedule of application, preharvest interval, and soil and weather conditions. Several measures were considered as means by which potential dietary exposure to the EBDCs and ETU through residues on food crops might be reduced.

a. Preharvest interval

The preharvest interval is the number of days that must elapse between the final application of a pesticide and actual harvest of the crop. Lengthening this interval provides more time for dissipation of residues before crops are harvested and ultimately consumed. Additionally, lengthening the preharvest interval can serve as a means of lowering tolerances. The practicality of extending the preharvest interval for the EBDCs cannot be evaluated at this time due to lack of efficacy data, but the Agency believes that extending the preharvest interval could be equivalent to cancellation on some crops because the crop could be unprotected from disease during the extended preharvest interval.

b. Modify Application Practices

Three modified application practices were considered to reduce EBDC and ETU exposure and risk through reduction in crop residues: 1) reducing the amount of active ingredient in the formulations, 2) reducing the amount of formulation applied per season and 3) reducing the amount of active ingredient applied per acre. Use rates, frequency and the number of applications per season are based on field evaluations carried out under various degrees of disease pressure, varying environmental conditions and in diverse geographic regions. The limited field trials available comparing application rates of EBDCs were reviewed by the Agency. These trials indicate that under the conditions tested, the higher rates tested tend to be more efficacious and for the very few trials that included a range of application rates and yield data, the higher rates seemed to provide higher yields. Fewer applications and lower rates can be used in some instances where predictive management models are available which take into account local climatic and disease conditions. However, such models are currently available for a small number of crops (Pelletier, 1989). Therefore, based on the information available, the Agency believes that mandated modification in application practices could potentially adversely impact the efficacy of EBDCs as plant control agents and could, for some crops, be equivalent to cancellation in terms of potential economic impact.

2. Measures to Reduce Exposure to Applicators, Mixer/Loaders and Fieldworkers

The potential risks to persons mixing and loading EBDC formulations, applying the pesticide to crops and working in the fields treated with the pesticides were estimated and are summarized in Table II-19 and II-20. Specific risk reduction measures were considered by the Agency:

a. Protective Clothing

Dermal and inhalation exposure to the EBDCs and ETU can occur when mixing, loading, maintaining application equipment, during application and at the time field workers enter treated fields to cultivate, apply other pesticides and harvest.

The Agency has evaluated the level of risk reduction gained and the costs of requiring protective clothing for all agricultural workers using EBDC fungicides. Protective clothing, comprised of coveralls worn over a long-sleeved shirt and long pants, chemical-resistant gloves, shoes, socks, goggles or a face shield, and a chemical-resistant apron is expected to reduce dermal exposure to mixer/loaders by 40 percent and to applicators by 65 percent. The coveralls are not intended to be chemical-resistant. Since inhalation exposure is estimated to be 1-2 percent of the total exposure, and therefore, considered negligible, the need for respirators was not considered.

The costs of this protective clothing for workers (mixers, loaders, and applicators) applying maneb, mancozeb, and metiram to agricultural crops are estimated to be $25 to $37 per worker for approximately 30,000 to 40,000 workers or $0.75 to $1.5 million in total (Dumas, 1989). Costs for nabam and zineb are not included because nabam registrants have requested voluntary cancellation of all agricultural food uses of nabam and the sole technical producer of zineb has requested voluntary cancellation. However, the Agency believes that most persons applying EBDC fungicides probably use other pesticides which require the use of similar or even more restrictive protective equipment. Therefore, the Agency believes that the actual cost of requiring protective clothing of all agricultural workers applying EBDCs would be considerably lower than $1.5 million.

b. Reentry Intervals

Establishing a reentry interval would allow time for further breakdown of EBDC residues into ETU and ETU into metabolites or compounds of less concern. EBDCs meet both the chronic toxicity and exposure criteria specified in 40 CFR 158.140 for reentry data. The Agency considered requiring a reentry interval for all agricultural workers using EBDC fungicides. Presently, the Registration Standards for maneb, mancozeb, metiram and nabam specify an interim 24-hour reentry interval be placed on labels of all maneb, mancozeb, metiram and nabam end-use products registered for agricultural use. This interim level will remain in effect until dislodgeable foliar residue data required in the Registration Standards and in the March 1989 EBDC Data Call In are submitted, reviewed, and the Agency announces any change in this reentry interval. These data are due to EPA in July 1990. Since the Agency does not currently have data on deterioration of the EBDCs or ETU over time, it has no additional basis on which to propose a product specific reentry interval other than the interim reentry interval previously discussed.

The Agency has little data available on the costs imposed on agriculture from requiring a reentry interval for agriculture workers. However, the Agency believes that there would be little if any impact from a 24-hour reentry interval because workers could reenter a treated area within 24-hours if they wore the protective clothing required for applicators.

3. Measures to Reduce Industrial Worker Exposure

The nabam Registration Standard specified protective clothing requirements of long sleeved shirts, long pants, chemical-resistant gloves, shoes, socks and goggles or a face shield while mixing, loading or applying as well as a chemical-resistant apron when mixing and loading. Although low MOSs/MOEs (Margins of Safety/Margins of Exposure) for thyroid effects were calculated for nabam's use in sugar and paper mills, they were calculated based on surrogate agricultural data which are believed to yield higher exposure estimates. Because the surrogate exposure data may overestimate exposure, the Agency believes that once nabam-specific exposure data are submitted (due to be submitted in March, 1990), all thyroid MOSs/MOEs for nabam may increase above 100.

E. RISK/BENEFIT ANALYSIS OF REGULATORY OPTIONS

OPTION 1 - Continuation of Registration Without Changes

If the registrations for mancozeb, maneb, metiram and nabam for use on food crops, non-food crops and industrial sites were continued without restriction, the estimated total upper-bound ETU dietary risk would be 10^{-4} with cumulative forgone benefits of $46 to $75 million in producer impacts and $90 to $305 million in efficiency impacts. This risk would be higher if uses of zineb also were allowed to continue. The total risk was estimated by multiplying the estimated exposure by a carcinogenic potency factor, the Q_1*. Exposure was estimated using anticipated residue data, percent of crop treated data, and food consumption data from the USDA 1977-78 Nationwide Food Consumption Survey.

Also, there would be low MOS/MOEs (below 100) for thyroid and developmental effects and/or high cancer risks for mixer/loaders and applicators using maneb on grapes and commercial ornamentals, and on homeowner turf, fruit trees, vegetables and ornamentals; mancozeb on homeowner turf and fruit trees; and nabam in sugar and paper mills. Benefits are low for these uses because of the availability of alternatives.

OPTION 2 - Continuation of Registrations with Modifications to the Terms and Conditions of Registration.

Because of the lack of data, the Agency does not know whether amending the terms and conditions of registration by extending pre-harvest intervals or modifying application rates or practices would reduce the total dietary risk to a significant extent. The Agency believes that such modifications possibly may reduce the versatility and efficacy of EBDC products and thereby reduce their potential benefits. The March 1989 Data Call-In Notice required use information on the EBDCs which was submitted in August, 1989. Information on the percent of crop treated was used along with other available data in conducting the analyses used for the preliminary determination; most of the submitted data on comparative efficacy previously were available to the Agency, but any new information will be included in the final decision. This information and any other available information will be used to further refine the risk estimates for the Agency's Final Determination PD 4. Users and other groups are also encouraged to submit data demonstrating that application rate, frequency or other exposure variables can be modified to reduce overall exposure and still retain the efficacy of the products.

When estimating exposure to mixer/loader/applicators using EBDCs on agricultural sites, the Agency took into consideration protective clothing comprised of coveralls worn over a shirt and pants, chemical-resistant gloves, shoes, socks, goggles or a face shield for applying plus a chemical-resistant apron when mixing and/or loading EBDC pesticides. With incorporation of these additional protective clothing requirements, a few maneb MOSs/MOEs remained under 100: grapes and commercial ornamentals. The estimated carcinogenic risk to mixer/loader/ applicators from the risk of maneb products used on commercial ornamentals is 10^{-3}. No additional protective clothing or equipment appear practical to reduce these exposures further.

The Agency finds it impractical to enforce a requirement for protective clothing for homeowner uses as the Agency believes that homeowners are not likely to go to the added expense of buying, for example, gloves and goggles or a face shield considering the small amount of EBDC products used on home gardens and turf. MOS/MOEs for homeowners applying maneb on turf are below 100. Estimated carcinogenic risks to homeowners using maneb are greater than 10^{-6} for all uses; estimated risks to homeowners using mancozeb are greater than 10^{-6} for turf and fruit tree uses.

OSHA regulations, 29 CFR section 1910.132, already require industrial workers to use protective clothing and protective clothing requirements specified in the nabam Registration Standard are on nabam labels. MOS/MOEs for workers using nabam in sugar and paper mills are estimated to remain below 100 even when protective clothing is used. However, these estimates are based on exposure estimates which may need some refinement. The Agency's March 1989 EBDC Data Call-In Notice will provide nabam dermal exposure data for oil well drilling fluids and paper and sugar mills. These data are due to be received in March, 1990. To the extent that these data are available, they will be used to further refine the risk estimates for the Agency's Final Determination PD 4.

The interim 24-hour reentry interval for agricultural workers which is specified in the Registration Standards for maneb, mancozeb, metiram and nabam should reduce exposure of agricultural workers to EBDCs and ETU without imposing significant costs to the agricultural industry. Workers in greenhouses or field situations can reenter the treated area if they wear clothing specified for applicators. EBDC labels for products used on golf courses state that workers can reenter the treated area after the spray has dried. The Agency expects to receive dislodgeable foliar residue data in July 1990 which should allow the Agency to fully evaluate this risk reduction measure and determine whether any refinements are necessary.

OPTION 3 - Partial Cancellation

This option would propose cancellation of certain food and non-food uses. The goal of the option would be to reduce aggregate risks from EBDCs to a level that provides an appropriate overall balance of risks and benefits. In evaluating which uses should be cancelled, the Agency initially focussed on those uses which registrants seem unwilling to support. At this time, no registrant of zineb has indicated an interest in supplying the outstanding data for this chemical. All zineb uses currently are suspended (and have been for some time) and the only technical registrant has requested that the Agency cancel its registrations. Given the apparent lack of support for zineb, which the Agency believes is evidence of a lack of benefits provided by zineb, zineb uses were deemed least deserving of retention. Thus, under this option, the Agency would propose to cancel all zineb uses.

The Agency next turned to an examination of the 55 registered uses of maneb, mancozeb, and metiram. As noted earlier, the major technical registrants of mancozeb, maneb and metiram, recently requested that the Agency delete 42 of the 55 uses from their registrations. Maneb would be registered for use on almonds, bananas, potatoes, sugar beets and sweet corn; mancozeb would be registered for use on asparagus, bananas, cranberries, figs (caprifig only), grapes, onions, peanuts, potatoes, sugar beets, sweet corn, tomatoes and wheat; and metiram would be registered for use on potatoes. The registrants' action would decrease estimated upper-bound, carcinogenic risks from 4×10^{-4} to 2×10^{-5}. This action effectively places these 42 uses in a similar situation to the zineb uses--uses which appear to have been dropped by industry while technically remaining on the registrations of various formulators--and thus, under this option, these 42 uses would be proposed for cancellation.

Therefore, following the registrants' requested deletion of 42 uses, the Agency's analysis focussed on the risks and benefits of the thirteen crops retained by the registrants. These thirteen crops have an estimated upper-bound, cumulative excess lifetime risk of 2×10^{-5} and a cumulative benefit of $14 to $27 million in producer impacts. The Agency considered a risk-benefit balancing of each crop to determine whether the estimated dietary risk is reasonable. Using this analysis, EPA identified three crops (potatoes, tomatoes and bananas) with an unfavorable risk-benefit balance and accordingly, under this option, EPA would propose to cancel these three crops. This action would reduce the estimated lifetime cancer risk to 3×10^{-6} and would retain the maximum amount of benefits. Table IV-2 summarizes the crops which would be proposed for cancellation and retention under an option which assumed only the 13 registrant-retained crops remain registered.

Table IV-2

ESTIMATED RISKS AND BENEFITS OF CROPS WHICH WOULD BE PROPOSED FOR CANCELLATION AND RETENTION

A. 13 Crops Proposed to be Retained by Major EBDC Registrants

Proposed for Retention by EPA

Food crop	Estimated Excess Carcin. Risk[1]	Benefits
Almonds	7×10^{-9}	Not enough data to quantify; potential impacts
Asparagus	2×10^{-9}	Not enough data to quantify; potential impacts
Caprifigs	0	Not enough data to quantify; potential impacts
Corn, sweet	3×10^{-7}	$2.1 to $2.5 million producer impacts
Cranberry	5×10^{-7}	$0.1 million producer impacts
Grapes	9×10^{-7}	$1 to $3 million producer impacts
Onions	5×10^{-7}	$6.5 million producer impacts
Peanuts	2×10^{-8}	$2.4 million producer impacts
Sugar beet	1×10^{-6}	Not enough data to quantify; potential impacts
Wheat	1×10^{-7}	$1.6 to $11.7 million producer impacts
TOTAL	3×10^{-6}	$13 TO $26 million in producer impacts
Proposed for Cancellation by EPA		
Banana	1×10^{-6}	$0.3 million producer impacts in U.S.
Potatoes	2×10^{-6}	$0.4 million producer impacts
Tomato	2×10^{-5}	$0.1 million producer impacts

---

[1] Carcinogenic risk

Table IV-2 (Cont.)

ESTIMATED RISKS AND BENEFITS OF CROPS WHICH WOULD BE PROPOSED FOR CANCELLATION AND RETENTION

B. Crops Proposed to be Deleted from Registrations by Major EBDC Registrants which also would be cancelled under this option

Food Crop	Estimated Excess Carcin. risk	Benefits
Apples	1 x 10^{-4}	$0.3-$12.3 million producer impacts
Apricot	7 x 10^{-6}	Not enough data to quantify; minimal impacts expected
Barley	3 x 10^{-7}	$0.3 to $2.1 million producer impacts
Beans	3 x 10^{-5}	$1.9 to $ 2.1 million producer impacts
Beans, Lima	2 X 10^{-6}	$0.7 million producer impacts
Broccoli	1 X 10^{-5}	No impact expected
Brussels sprouts	4 X 10^{-7}	No impact expected
Cabbage	1 X 10^{-6}	No impact expected
Cantaloupe	3 X 10^{-7}	$0.3 million producer impacts
Casaba melons	6 x 10^{-9}	Not enough data to quantify; impacts expected
Crenshaw melons	<1 x 10^{-10}	Not enough data to quantify; impacts expected
Carrot	2 X 10^{-5}	$0.13 million producer impacts
Cauliflower	3 X 10^{-7}	No impact expected
Celery	2 X 10^{-5}	$1.3 to 3.4 million efficiency impacts
Collards	1 X 10^{-5}	Not enough data to quantify; impacts expected
Corn, field	7 x 10^{-8}	Not enough data to quantify; no impact expected
Cotton	6 x 10^{-8}	Not enough data to quantify; no impact expected
Crabapple & quince	6 x 10^{-7}	Not enough data to quantify; no impacts expected
Cucumbers	9 x 10^{-7}	$4.0 to $4.9 million producer impacts
Eggplant	3 x 10^{-8}	Not enough data to quantify; potential impacts
Endive	3 x 10^{-8}	Not enough data to quantify; potential impacts
Fennel	1 x 10^{-9}	Not enough data to quantify; no impacts expected
Honeydew melons	1 x 10^{-7}	Not enough data to quantify; impacts expected

Table IV-2 (Cont.)

ESTIMATED RISKS AND BENEFITS OF CROPS WHICH WOULD BE PROPOSED FOR CANCELLATION AND RETENTION

Food Crop	Estimated Excess Carcin. risk	Benefits
Lettuce	3×10^{-6}	$40 to $204 million efficiency impacts
Kale	7×10^{-7}	Not enough data to quantify; impacts expected
Kohlrabi	1×10^{-8}	Not enough data to quantify; impacts expected
Mustard greens	2×10^{-5}	Not enough data to quantify; impacts expected
Nectarines	1×10^{-6}	Negligible producer impacts
Oats	6×10^{-8}	$0.1 to $0.5 million producer impacts for oats & rye
Papaya	2×10^{-7}	Not enough data to quantify; no impacts expected
Peaches	4×10^{-5}	<$15,000 producer impacts
Pear	2×10^{-6}	Not enough data to quantify; minimal impacts expected
Pecan	4×10^{-10}	Not enough data to quantify; minimal impacts expected
Peppers	3×10^{-6}	$49 to $98 million in efficiency impacts
Pineapple	$<1 \times 10^{-10}$	Not enough data to quantify; potential impacts
Pumpkin	1×10^{-8}	$77,000 producer impacts
Rhubarb	7×10^{-7}	Not enough data to quantify; no impacts expected
Rye	4×10^{-9}	$0.1 to $0.5 million producer impact for oats & rye combined
Spinach	2×10^{-5}	$19 million producer impacts
Squash	3×10^{-7}	$3.4 to $4.8 million producer impacts
Turnip	2×10^{-5}	Not enough data to quantify; impacts expected
Watermelon	2×10^{-6}	$0.8 million producer impacts
TOTAL	3×10^{-4}	$32 to $58 million in producer impacts and $90 to $305 million in efficiency impacts

In summary, under this option the Agency would propose to cancel all uses of zineb and 45 uses of maneb, mancozeb and metiram reducing estimated lifetime cancer risk to 3 x 10^{-6} and retaining benefits of $13 to $26 million.

If the maneb, mancozeb and metiram registrants had not deleted 42 of 55 registered uses, the Agency would have pursued regulatory action based on a risk-benefit analysis of the 55 crop universe. While EPA believes it is appropriate to consider only the 13 remaining uses in its proposed action, the Agency is presenting its 55 crop analysis to (1) provide a full description of the risks and benefits of the EBDCs and (2) enable all affected parties to have the best information possible for purposes of commenting on the Agency's analysis and proposed action.

In assessing the risks and benefits of the 55 crops, ten crops yielded an estimated upper-bound, cumulative lifetime risk of 1 x 10^{-7} and benefits of $2.4 million. The crops are: almonds, asparagus, casaba melons, crenshaw melons, eggplant, endive, figs, peanuts, pineapple and pumpkin. Since these crops have some benefit and very low risk, they would have been proposed for retention if the registrants had taken no action. The remaining crops were then ranked in order of lowest risk/highest benefit or cost effectiveness ratios (See Table IV-3). The two crops with the highest benefits, lettuce and peppers, each have an estimated risk of 3 x 10^{-6}. The benefits from lettuce are $40 to $204 million in efficiency impacts and

Table IV-3

Cost-Effectiveness Estimates for EBDC Cancellation

Site	Incidents[1] Avoided	Benefit[2] Mil.Dol.	C-E[3] $Mil/Incident
Peanuts	0.1	2.4 - 2.4	43.75 - 43.75
Lettuce	10.3	40.0 - 205.0	3.89 - 19.93
Peppers	11.7	49.0 - 98.0	4.20 - 8.41
Onions	1.6	6.5 - 6.5	4.03 - 4.03
Wheat	2.9	1.6 - 11.7	0.55 - 4.01
Sweet corn	0.9	1.9 - 1.9	2.05 - 2.05
Cucumbers	3.2	4.0 - 5.0	1.27 - 1.59
Grapes	3.1	2.0 - 2.0	0.65 - 0.65
Other cucurbits	9.4	4.5 - 5.5	0.48 - 0.59
Spinach	51.4	19.0 - 19.0	0.37 - 0.37
Other small grains	24.0	0.4 - 2.6	0.02 - 0.11
Bananas	4.1	0.3 - 0.3	0.07 - 0.08
Potatoes	5.8	0.4 - 0.4	0.07 - 0.07
Cranberries	1.8	0.1 - 0.1	0.06 - 0.06
Celery	61.7	1.3 - 3.4	0.02 - 0.06
Apples	342.9	12.0 - 12.0	0.04 - 0.04
Beans	85.7	2.0 - 2.0	0.02 - 0.02
Tomatoes	54.9	0.1 - 0.1	0.00 - 0.00
Carrots	65.1	0.1 - 0.1	0.00 - 0.00
Leafy greens	163.6	No estimate	

---

[1] Estimated annual cancer cases from consumption of the particular crop. Based on estimated dietary risk for U.S. population using assumptions described in Chapter II.

[2] Estimated annual benefits for the particular crop using assumptions described in Chapter III.

[3] Loss in economic benefits per case avoided.

the estimated benefits from peppers are \$49 to \$98 million inefficiency impacts. However, if both crops were retained, the cumulative dietary risk from the two crops alone is 6×10^{-6}. Of the two, lettuce has the higher estimated benefit. The other two crops which have a favorable risk/benefit ratio are onions (with an estimated excess risk of 5×10^{-7} and \$6.5 million in producer impacts) and cucumbers (with an estimated risk of 9×10^{-7} and \$4 to \$4.9 million in producer impacts). The cumulative estimated upper-bound lifetime risk from the ten negligible risk crops as well as lettuce, onions and cucumbers is 5×10^{-6}. The cumulative estimated benefits are \$13 to \$14 million in producer impacts and \$40 to \$204 in efficiency impacts.

If peppers were included, the total estimated risk would be 8×10^{-6}. Total estimated benefits would be \$13 to \$14 million in producer impacts and \$89 to \$302 million in efficiency impacts. Even though the individual benefits for peppers were high, the Agency was concerned that the risk contribution of pepper to the aggregate dietary risk was excessive.

The Agency also considered retaining spinach since the benefits are high with an estimated 70 percent of the winter spinach crop potentially affected and economic impacts projected to be \$19 million. However, the Agency decided that although benefits appeared to be high for this relatively minor crop, the estimated ETU dietary risk of 10^{-5} for spinach outweighed the benefits.

Forty-two food crops or crop groupings would have been proposed for cancellation in the absence of the registrants' action. The following Table IV-4 summarizes the estimated dietary risks and benefits of the food crops which would be proposed for cancellation.

For all crops proposed for cancellation and particularly for peppers and spinach, the Agency requests comments on its risk/benefit analysis. In addition, EPA seeks information or whether changes in use practices could reduce risk to an acceptable level.

Table IV-4

ESTIMATED RISKS AND BENEFITS OF EBDC CROPS WHICH WOULD HAVE BEEN PROPOSED FOR CANCELLATION IN THE ABSENCE OF REGISTRANT ACTION

Food Crop	Estimated excess Carcin. risk [1]	Benefits
Apples	1 x 10^{-4}	\$0.3-\$12.3 million producer impacts
Apricot	7 x 10^{-6}	Not enough data to quantify; minimal impacts expected
Banana	1 x 10^{-6}	\$0.3 million producer impacts in U.S.
Barley	3 x 10^{-7}	\$0.3 to \$2.1 million producer impacts
Beans	3 x 10^{-5}	\$1.9 to \$ 2.1 million producer impacts
Beans, Lima	2 X 10^{-6}	\$0.7 million producer impacts
Broccoli	1 X 10^{-5}	No impact expected
Brussels sprouts	4 X 10^{-7}	No impact expected
Cabbage	1 X 10^{-6}	No impact expected
Cantaloupe	3 X 10^{-7}	\$0.3 million producer impacts
Carrot	2 X 10^{-5}	\$0.13 million producer impacts
Cauliflower	3 X 10^{-7}	No impact expected
Celery	2 X 10^{-5}	\$1.3 to 3.4 million efficiency impacts
Collards	1 X 10^{-5}	Not enough data to quantify; impacts expected
Corn, field	7 x 10^{-8}	Not enough data to quantify; no impact expected
Corn, sweet	3 x 10^{-7}	\$2.1 to \$2.5 million producer impacts
Cotton	6 x 10^{-8}	Not enough data to quantify; no impact expected
Crabapple & quince	6 x 10^{-7}	Not enough data to quantify; no impacts expected
Cranberry	5 x 10^{-7}	\$0.1 million producer impacts
Fennel	1 x 10^{-9}	Not enough data to quantify; no impacts expected
Grapes	9 x 10^{-7}	\$1 to \$3 million producer impacts
Honeydew melons	1 x 10^{-7}	Not enough data to quantify; impacts expected
Kale	7 x 10^{-7}	Not enough data to quantify; impacts expected
Kohlrabi	1 x 10^{-8}	Not enough data to quantify; impacts expected
Mustard greens	2 x 10^{-5}	Not enough data to quantify; impacts expected
Nectarines	1 x 10^{-6}	Negligible producer impacts

Table IV-4 (Cont.)

ESTIMATED RISKS AND BENEFITS OF EBDC CROPS WHICH WOULD HAVE BEEN PROPOSED FOR CANCELLATION IN THE ABSENCE OF REGISTRANT ACTION

Food Crop	Estimated Excess Carcin. risk	Benefits
Oats	6×10^{-8}	\$0.1 to \$0.5 million producer impacts for oats & rye
Papaya	2×10^{-7}	Not enough data to quantify; no impacts expected
Peaches	4×10^{-5}	<\$15,000 producer impacts
Pear	2×10^{-6}	Not enough data to quantify; minimal impacts expected
Pecan	4×10^{-10}	Not enough data to quantify; minimal impacts expected
Peppers	3×10^{-6}	\$49 to \$98 million in efficiency impacts
Potatoes	2×10^{-6}	\$0.4 million producer impacts
Rhubarb	7×10^{-7}	Not enough data to quantify; no impacts expected
Rye	4×10^{-9}	\$0.1 to \$0.5 million producer impact for oats & rye combined
Spinach	2×10^{-5}	\$19 million producer impacts
Squash	3×10^{-7}	\$3.4 to \$4.8 million producer impacts
Sugar beet	1×10^{-6}	Not enough data to quantify; potential impacts
Tomato	2×10^{-5}	\$0.1 million producer impacts
Turnip	2×10^{-5}	Not enough data to quantify; impacts expected
Watermelon	2×10^{-6}	\$0.8 million producer impacts
Wheat	1×10^{-7}	\$1.6 to \$11.7 million producer impacts
TOTAL	3×10^{-4}	\$32 to \$58 million in producer impacts and \$90 to \$305 million in efficiency impacts

The following Table IV-5 summarizes the estimated dietary risks and benefits of the food crops which would have been proposed for retention if the registrants had not taken no action.

Table IV-5

ESTIMATED RISKS AND BENEFITS OF EBDC CROPS WHICH WOULD HAVE BEEN PROPOSED FOR RETENTION IN THE ABSENCE OF REGISTRANT ACTION

Food crop	Estimated Excess Carcin. Risk[1]	Benefits
Almonds	7×10^{-9}	Not enough data to quantify; potential impacts
Asparagus	2×10^{-9}	Not enough data to quantify; potential impacts
Caprifigs	0[2]	Not enough data to quantify; potential impacts
Casaba melons	6×10^{-9}	Not enough data to quantify; impacts expected
Crenshaw melons	$<1 \times 10^{-10}$	Not enough data to quantify; impacts expected
Cucumbers	9×10^{-7}	\$4.0 to \$4.9 million producer impacts
Eggplant	3×10^{-8}	Not enough data to quantify; potential impacts
Endive	3×10^{-8}	Not enough data to quantify; potential impacts
Lettuce	3×10^{-6}	\$40 to \$204 million efficiency impacts
Onions	5×10^{-7}	\$6.5 million producer impacts
Peanuts	2×10^{-8}	\$2.4 million producer impacts
Pineapple	$<1 \times 10^{-10}$	Not enough data to quantify; potential impacts
Pumpkin	1×10^{-8}	\$77,000 producer impacts
TOTAL	5×10^{-6}	\$13 to \$14 million in producer impacts and \$40 to \$204 million in efficiency impacts

---

[1] Carcinogenic risk

[2] Registrant has voluntarily cancelled use directly on food crop; only use remaining is on caprifig which is unlikely to result in any residue

For risks to mixer/loaders and applicators, the Agency would also propose cancellation of all sites associated with unacceptable MOSs/MOEs (those under 100 with low benefits) after incorporation of additional protective clothing requirements for workers and without additional protective clothing for homeowners which EPA considers impractical. In these cases, EPA believes risks outweigh benefits. In addition, the Agency would propose cancellation of all sites with estimated upper-bound, carcinogenic risks to mixer/loader/applicators exceeding 10^{-4} for workers after incorporation of additional protective clothing and exceeding 10^{-6} for homeowners without additional protective clothing. Additional protective clothing requirements are not considered practical for homeowners. Registrations bearing the following uses would be affected: (1) maneb on homeowner vegetables, ornamentals, fruit trees and turf sites and on grapes and commercial ornamentals; (2) mancozeb on homeowner fruit trees and turf sites; and (3) nabam in sugar and paper mills. See Table IV-6. Again, the Agency believes risks outweigh benefits.

OPTION 4 - Cancellation of all registrations

If the registrations of the EBDCs for all food uses were cancelled, all dietary carcinogenic risks to persons from the consumption of EBDC-treated foods would be eliminated and all developmental and thyroid risks to mixer/loader/applicators from the use of EBDCs on food crops would be eliminated. The cancellation of the registrations for maneb, mancozeb, metiram, and nabam would have an estimated \$46 to \$75 million in producer

Table IV-6

Summary of M/L/A MOSs/MOEs for Developmental and Thyroid Effects and/or Carcinogenic Risks and Benefits for Sites Proposed for Cancellation

Site	Estimated Risks	Benefits
Maneb		
. Grapes	20 (TE)	\$1 to \$3 million producer impact
. Comm. Ornamentals	6 (TE)	Minimal impacts. Alternatives available.
. Homeowner Uses		
Fruit trees	10^{-4} (CR)	Minimal use. Alternatives available.
Ornamentals	10^{-5} (CR)	
turf	60 (DE) 10^{-4} (CR)	
. vegetables	10^{-5} (CR)	
Nabam		
. Sugar Mills	75 (TE)	\$0.4 - \$0.5 million increase for alternatives
. Paper Mills	75 (TE)	Alternatives less expensive.

CR = Carcinogenic Risks
DE = Developmental Effects
TE = Thyroid Effects

impacts and $90 to $305 million in efficiency impacts the first year following cancellation. Benefits from zineb are assumed to be minimal based on the lack of support for these uses. With full cancellation, EPA also would revoke all food tolerances so that residues in imported as well as domestic crops would be unlawful. Under this option, uses on many crops with negligible estimated risks (10^{-10} to 10^{-7}) would be treated the same as uses on crops with high estimated risks. In addition, cancellation of EBDC registrations on many minor crops with no alternatives would result in some growers experiencing severe impacts.

If registrations of the EBDCs for non-food crops, commercial, homeowner and industrial uses were cancelled, all mixer/loader/applicator carcinogenic, thyroid and developmental risks from EBDCs or ETU exposure would be eliminated. Cancellation of maneb, mancozeb, metiram, and nabam on these use sites would have a $5 to $15 million impact in the first year following cancellation.

V. PROPOSED REGULATORY OPTIONS

The Agency believes that the estimated aggregate risk from all of the EBDCs is unacceptably high. The level of estimated benefits, $46 to $75 million in producer impacts and $90 to $305 million in efficiency impacts in the first year, cannot justify an estimated dietary risk in the range of 10^{-4}. At the same time, the Agency does not think that full cancellation is warranted in light of the estimated benefits of continued maneb, mancozeb and metiram use on some crops, and the low estimated carcinogenic, developmental and thyroid risks associated with certain of the individual crops. Consequently, the Agency proposes a partial cancellation of EBDC registrations combining options 2 and 3 - partial cancellation of registrations and continuation of other registrations with modifications to the terms and conditions of registration. The goal of this proposal is to reduce aggregate risks from EBDCs to a level that provides an appropriate overall balance of risks and benefits. Specific proposed regulatory actions are outlined below.

EPA tentatively plans not to issue a final decision until the Agency has had the opportunity to examine market basket data due to be submitted in September 1990. Dietary risk estimates presented in this document were based on field residue data which may well overestimate actual dietary risk. The Agency believes that a well designed and properly conducted food residue monitoring study may more accurately estimate ETU residues "at the dinner plate" and could support risk estimates of as much as one or two orders of magnitude lower than our current risk estimates for some crops, at which point estimated benefits could exceed risks for additional food crops than those currently proposed for retention.

Due to lack of more refined data, developmental and thyroid MOSs/MOEs for mixer/loaders and applicators were based on upper-bound exposure estimates. Although many of the resulting MOSs/MOEs are of concern (<100), and risks are unreasonable because benefits are low, the Agency believes that actual dermal exposure and absorption data may increase these MOSs/MOEs. However, as to both dietary and mixer/loader/applicator risk issues, in the absence of data sufficient to demonstrate lower exposure, currently available data will be used to make the Final Determination risk estimates. In that event, as discussed in this document, estimated risks outweigh estimated benefits for many uses.

Due to the assumptions surrounding dietary and mixer/loader/applicator risks, the Agency has required additional data through FIFRA section 3(c)(2)(B) to further refine risk estimates. The Agency plans to issue the PD 4 in the spring of 1991 to allow review and consideration of new exposure data that should become available which the Agency currently believes could result in a more refined risk/benefit assessment of the EBDCs and ETU.

A. Food Crop Uses

In deciding which food uses to retain, the Agency considered a range of factors. Where the market situation has indicated a lack of support for a particular use, the Agency is proposing to cancel that use without further detailed analysis. Cancellation is necessary despite the actions by the technical registrants because the uses the technical registrants have requested deleted remain on the registrations of various formulators. For uses which the technical registrants have retained, the Agency has examined the risks and benefits of each use, to the extent that information is available, in evaluating which uses should be cancelled and which retained.

All zineb uses and the 42 uses dropped by the technical registrants of mancozeb, maneb, and metiram are proposed for cancellation on the basis of unacceptable risk and a lack of support by registrants. It will be difficult for end use formulators to retain the uses dropped by the technical registrants. Not only will the formulators need to arrange an alternate source of supply, but they will also need to generate a substantial amount of data to support registration of these uses. The Agency believes the action taken by the technical registrants has altered the market sufficiently that it is appropriate to consider that only the 13 crops will remain. Thus, the Agency's proposed cancellation, in a practical sense, reflects what has, by and large, already taken place.

Cancelling all zineb uses and the 42 uses of mancozeb, maneb and metiram dropped by the registrants leaves thirteen food crop uses: tomatoes, potatoes, bananas, grapes, wheat, cranberries, onions, sugar beets, sweet corn, peanuts, almonds, asparagus and figs. These crops have an estimated upper-bound, cumulative lifetime risk of 2×10^{-5} and an estimated cumulative benefit of \$14 to \$27 million in producer impacts (see Table IV-2).

The Agency believes the level of estimated upper-bound, risk associated with these thirteen crops outweighs the associated benefits. Thus, the Agency finds that action beyond that taken by the registrants is necessary to reduce risks to acceptable levels. The Agency considered a risk-benefit balancing of each crop to determine which crops had estimated benefits which exceeded the estimated risks and yielded an acceptable cumulative dietary risk. The Agency determined that ten crops met this test. These are: grapes, wheat, cranberries, onions, sugar beets, sweet corn, peanuts, almonds, asparagus and figs. These ten crops have an estimated upper-bound, cumulative risk of 3×10^{-6} and cumulative benefits of \$13 to \$26 million in producer impacts. Therefore, the Agency proposes to cancel three more crops in addition to the 42 already discussed. These three crops are tomatoes, potatoes and bananas. Tomatoes have an estimated risk of 2×10^{-5} and estimated benefits of only \$0.1 million. Potatoes and bananas each have estimated risks in the 1×10^{-6} range but less than \$0.5 million in estimated benefits. None of the three crops appears to have sufficient benefits to exceed these levels of estimated risks, particularly when it is recognized that these risks need to be added to risks from other crops to estimate total dietary risk.

In determining the appropriate regulatory action, the Agency considered the interim dietary risk while the Special Review is being conducted. When estimating excess lifetime cancer risk over a 70 year lifespan, EPA calculates one risk number for the general population. This estimate takes into account that a person moves from infancy through childhood and into being an adult, and that consumption patterns change with these different stages. However, when considering a time period of a few years, EPA calculates risk numbers for both the overall population and the most sensitive subpopulations. These estimates are estimated lifetime cancer risks resulting from exposure during the short time period, and take into account the different types and amounts of food typically consumed by each subgroup.

EPA calculated the estimated interim dietary risks for three groups--overall population, non-nursing infants and younger children 1 to 6 years of age. In estimating the risks, the Agency used the following assumptions: (1) the time period to complete the Special Review will be two years (the PD 4 is now scheduled for the spring of 1991); (2) no zineb use will occur during this period (all registrants are suspended and the one technical registrant has requested voluntary cancellation); and (3) mancozeb, maneb and metiram will be used on only 13 crops (the four technical registrants control over 90 percent of the market and all their products will be labeled only for 13 uses after January 1, 1990.)

If all 13 crops are available for two more years, EPA estimates the incremental risk to the general population would be 7×10^{-7}. The risk to infants would be 1×10^{-6} and the risk to children aged one to six would be 1×10^{-6}. Given that these estimates are upper-bound risk numbers (the true risk is just as likely to be zero as it is to be the upper-bound number), EPA believes the risks are acceptable.

The interim risks would increase slightly if EPA's final decision is delayed by a cancellation hearing. At the same time, EPA's risk numbers are likely to be overestimates because they are based on field trial data rather than market basket data. Existing monitoring data, while not sufficient to base regulatory decisions on, show a clear pattern of being one to two orders of magnitude less than field trial data. Registrants are now conducting a market basket survey in an effort to show that residue levels on fruits and vegetables are lower in the grocery store than shown in field trials.

If other registrants attempt to support and maintain any of the 42 food uses which the four technical registrants have dropped from their label, EPA will consider these uses and determine whether any additional risk are acceptable. The Agency plans to closely monitor the marketplace over the next two years and will take whatever action is necessary to maintain acceptable interim risks.

As soon as some or all of the 42 crops are cancelled by all registrants, EPA will finalize tolerance revocations on those uses to remove exposure from imported crops as well as domestic ones. Prior to revocation, the uses of EBDCs on imported food would slightly increase interim risk.

Additional data from toxicological and exposure studies are expected to be received by EPA. If any information raises concerns about interim risk, the Agency is prepared to initiate prompt, further regulatory action.

In identifying crops for retention of registration, the Agency considered the feasibility of modifications to reduce dietary risk, such as lengthening pre-harvest intervals, limiting application frequencies, or lowering application rates. However, due to the lack of information, the Agency could not assess the feasibility of these measures. Without data, it is difficult to determine if the pesticide would be efficacious under these varying conditions. The Agency is interested in comments and data which will help the Agency consider this option more carefully in the Final Determination. Commenters need to specify label modifications and provide either data or analysis to show that the EBDC pesticides could be used efficaciously in accordance with such rates and practices. Even though the comment period ends 90 days after publication of this Notice, the Agency will likely accept residue data through the summer of 1990 when the Market Basket survey is due. Residue data showing residues resulting from differing application rates or frequencies or pre-harvest intervals will be needed to show the risk reduction impact of these measures. To ensure that studies provide adequate, valid data, EPA urges that protocols and study parameters be discussed with the Agency before studies are initiated.

In conducting the risk-benefit analysis for each crop, the Agency considered the estimated risks posed by alternatives, based on currently available data. In preparing the Final Determination, the Agency will consider not only new data received on the EBDCs but also new data received on the significant alternatives and consider the estimated risks and benefits of EBDC use on each crop in light of the estimated risks and benefits posed by alternative pesticides. The Agency specifically requests comment on the benefits for each crop and on which alternatives are likely to be used.

B. Tolerances

Within 90 days of the issuance of this document, the Agency intends to propose tolerance revocations for the 45 food uses of maneb, mancozeb and metiram and all (58) food uses of zineb proposed for cancellation in this Preliminary Determination. The Agency presently intends to finalize the tolerance actions, reflecting consideration of public comments, when all products for particular uses are voluntarily cancelled, or the Agency issues the Final Determination, whichever occurs earlier. In issuing final rules to revoke tolerances, the Agency will set tolerance expiration dates which take into consideration any crops which were treated legally before the effective date of the cancellation. Tolerances for retained uses will be reevaluated once the Agency receives metabolism and residue data required under the EBDC Comprehensive Data Call-Ins and Registration Standards. Any necessary adjustments to raise or lower existing tolerances will be proposed at that time.

C. Non-Industrial Uses

The Agency proposes a label language requirement that commercial agricultural workers (M/L/A) applying EBDC pesticides wear coveralls over long-sleeved shirt and long pants, chemical-resistant gloves, shoes, socks, and goggles or a face shield. Additionally, during mixing and loading, a chemical-resistant apron must be worn. For agricultural workers, where completely enclosed cabs with positive pressure filtration, or an enclosed cockpit for aerial application are used, a long-sleeve shirt and long pants may be worn in place of the protective clothing described above. Chemical-resistant gloves must be available in the cab or cockpit and worn upon exiting. During aerial application, human flaggers are prohibited unless in totally enclosed vehicles. With incorporation of the above-mentioned protective clothing requirements, MOSs/MOEs for workers using EBDC products on agricultural sites would all increase above 100 except for maneb use on grapes and ornamentals which are proposed for cancellation because EPA has determined that risks exceed benefits.

The Agency estimates that the cost of the above protective clothing would range from $0.75 to $1.5 million if every commercial agricultural user of EBDC pesticides needed to buy the protective equipment. However, the Agency believes the costs of this requirement would actually be much lower because most growers already own such equipment as it is required for use when applying a number of other agricultural chemicals.

The Agency proposes a label language requirement establishing an interim reentry interval of 24 hours for all EBDC products used on agricultural sites. This interim reentry interval will remain in effect until dislodgeable foliar residue data (showing EBDC and ETU exposure to agricultural workers reentering treated fields for the purposes of hand harvesting, pruning, weeding, etc.) required in the EBDC Registration Standards and as required in the March 1989 EBDC Data Call-In Notice are submitted and evaluated. These data are due to be submitted in July 1990. The Agency believes that there would be little if any economic impact from this requirement.

The Agency proposes a label language requirement that homeowners applying EBDC pesticides wear a long-sleeved shirt and long pants and rubber gloves. Gloves must be washed thoroughly with soap and water befor removing; clothes must be changed immediately after using the EBDC product and laundered separately from other laundry items before reuse. Homeowners applying EBDCs must shower immediately after use. The Agency did not consider that additional protective clothing requirements for homeowners would be a viable means of reducing risks because the Agency believes that homeowners will not go to the expense of purchasing or wearing protective clothing. Therefore, EPA proposes to cancel the use of maneb on turf by homeowners where MOSs/MOEs are under 100, and risks outweigh benefits.

In addition, because millions of households have gardens and many more have lawns which could be treated, the Agency is concerned about estimated cancer risks which exceed 10^{-6} for homeowners applying EBDCs. EPA believes such risks exceed the benefits of use. Homeowner sites which have estimated risks exceeding 10^{-6} are: (1) mancozeb on fruit trees and turf and (2) maneb on vegetables, ornamentals, fruit trees and turf. See Table II-19. Little or no economic impact is expected because home gardeners can switch from maneb to mancozeb for vegetables and ornamentals and can use captan on fruit trees instead of EBDCs. The Agency estimates that less than one percent of residential lawns are treated with EBDCs and any impact would be negligible. Therefore, EPA proposes to cancel homeowner use of mancozeb on fruit trees and turf, and homeowner use of maneb on vegetables, ornamentals, fruit trees and turf.

D. Industrial Uses

The Agency proposes a label language requirement that all industrial workers (M/L/A) applying EBDC pesticides wear coveralls over long-sleeved shirt and long pants, chemical-resistant gloves, shoes, socks, and goggles or a face shield. Additionally, during mixing and loading, a chemical-resistant apron must be worn. Similar label language already appears on nabam labels and OSHA requires protective clothing when applying hazardous chemicals under 29 CFR §1910.132; therefore, the Agency believes there would be minimal costs resulting from this requirement.

The Agency proposes cancellation of nabam use in paper mills and sugar mills based on thyroid MOSs/MOEs below 100 due to occupational exposure after incorporation of protective clothing requirements listed above. EPA has determined that risks outweigh benefits in these cases. If nabam's use were cancelled, the cost to the paper industry would increase by $700,000. There are three alternatives for nabam's use in sugar mills. The most viable alternative (Busan) possibly would increase production costs between $400,000 to 500,000 if it replaced nabam.

VI. REFERENCES

Abbott, et al. (1987). "Worker Exposure to a Herbicide Applied with Ground Sprayers in the United Kingdom," Am. Ind. Hyg. Assoc. Journal 48(2), 167-175.

Backus, Byron T. (September 2, 1988). "Public Comments on Nabam." Hazard Evaluation Division, Toxicology Branch, Office of Pesticide Programs, USEPA. 3 pp. (with attachments).

Balin, P.N. (1970). "Experimental Data on the Blastomogenic Activity of the Fungicide Maneb," Vrach. Delo. 4:21-24.

Ballard, Gary L. (June 7, 1988). "Number of Applications for EBDC Fungicides on Food Crops." Benefits and Use Division, Office of Pesticide Programs, USEPA. 3 pp.

Ballard, Gary L. (June 28, 1988). "Projections of Percent Crop Treated by Fungicides for Different Regulatory Scenarios." Benefits and Use Division, Office of Pesticide Programs, USEPA. 6 pp.

Battelle Columbus Laboratories. (1982). "Report on Maximum Neonatal Dose Studies with Ehtylenethiourea." (Contract No. NO1-ES-2151, to National Institute of Environmental Health Sciences, January 29, 1982).

Campt, D.D. (September 21, 1988). "Fungicide Review Strategy for Captan, Chlorothalonil and the EBDCs." Office of Pesticide Programs, USEPA. 12 pp.

Chernov, O.V. et al. (1969). "Blastomogenic Properties of Certain Derivatives of Dithiocarbamic Acids (zineb and ziram herbicides)," Vprosy Ongolog. 15(4):7-74.

Copplestone et al. (1976). "Exposure to Pesticides in Agriculture: A Survey of Spraymen Using Dimethoate in the Sudan," Bull. World Health Organ. 54:217-223.

Couoshee, R.J. (1967). "Application and Use of Foliar Fungicides," in Fungicides, An Advanced Treatise, D.C. Torgeson, ed. Academic Press, New York.

Dearfield, Kerry L. (September 25, 1989). "Comments on the Mutagenicity of EBDCs Based on Available Studies." Toxicology Branch, Office of Pesticide Programs, USEPA. 23 pp.

Dearfield, Kerry L. (July 22, 1988). "Response to Rohm and Haas Evaluation of Ethylene Thiourea (ETU) for Genetic Activity." Toxicology Branch, Office of Pesticide Programs, USEPA. 21 pp.

Diem, K. and C. Lentner (Editors). (1975). Documenta Geigy, Scientific Tables, 7th Edition, Geigy Pharmaceuticals,, Division of Ciba-Geigy Corporation, Ardsley, NY. pp. 693-705 .

Dowler, W.H. (September 7, 1978). ARS, USDA, Beltsville, Md. Personal Communication to E.N. Pelletier, EPA, Washington, D.C.

DPRA (1988a). Analysis of Possible Economic Effects of Cancelling Certain Fungicides for Seed Treatment. Manhattan, KS.

DPRA (1988c). Analysis of Possible Economic Effects of Cancelling Certain Fungicides on Cucurbits. Manhattan, KS.

DPRA (1988c). Analysis of Possible Economic Effects of Cancelling Certain Fungicides for Non-Agricultural Uses. EPA Contract Report 68-02-4272.

Evans, E. (1977). "The Theory and Practice of Applying Foliar Fungicides," in Antifungal Compounds, Vol. 1, M.R. Siegal and H.D. Sisler, eds., Marcel Dekker Inc., N.Y.

Everhart, Leighton P. and Richard F. Holt. (1982). "Potential Benlate Fungicide Exposure During Mixer/Loader Operations, Crop Harvest and Home Use," J. Agric. Food Chem., Vol. 30: 222-227.

Firestone, Michael P. (April 15, 1988). "Analysis of EBDC PD-1 Rebuttal Comments on Mancozeb (Rohm and Haas)." Non-Dietary Exposure Branch, Health Effects Division, USEPA. 68 pp.

Firestone, Michael P. (August 17, 1988). "Review of Mushroom Worker Exposure Study." Non-Dietary Exposure Branch, Health Effects Division, USEPA. 4 pp.

Firestone, Michael P. (October 14, 1988). "EBDC Formulations Stability in Tank Mixes - Request for Data." Non-Dietary Exposure Branch, Health Effects Division, USEPA. 2 pp.

Foy, W.E. (1977). "Fungicides in Perspective" in Antifungal Compounds, Vol.1, M.R. Siegal and H.D. Sisler, eds., Marcel Dekker, Inc., N.Y.

Freudenthal et al. (1977). "Dietary Subacute Toxicity of Ethylenethiourea in the Laboratory Rat," J. Environ. Path. Tox. 1:147-161.

Graham, S.L., K.J. Davis, W.H. Hansen and C.H Graham (1975). "Effects of Prolonged ETU Ingestion on the Thyroid of the Rat," Food Cosmet. Toxicol. 13: 493-99.

Graham, S.L., W.H. Hansen, K.J. Davis and C.H. Perry (1973). "Effects of One-Year Administration of Ethylenethiourea upon the Thyroid of the Rat," J. Agr. Food Chem. 21:324-329.

Hauswirth, Judith W. (December 2, 1986). "Peer Review of Ethylenethiourea." Hazard Evaluation Division, Office of Pesticide Programs, USEPA. 14 pp.

Hauswirth, Judith W. (May 25, 1988). "Mancozeb-Review of Liver Slides from Innes Study on ETU (Rohm and Haas)." Hazard Evaluation Division, Office of Pesticide Programs, USEPA. 3 pp.

Hauswirth, Judith W. (June 16, 1988). "Metiram-Registrant Response to Agency PD-1 (BASF Corporation)." Hazard Evaluation Division, Office of Pesticide Programs, USEPA. 2pp.

Hauswirth, Judith W. (July 14, 1988). "Mancozeb-Registrant Response to Agency PD-1 (Rohm and Haas)." Hazard Evaluation Division, Office of Pesticide Programs, USEPA. 3pp.

Hauswirth, Judith W. (July 14, 1988). "Maneb-Registrant Response to Agency PD-1 (Pennwalt Chemical Corporation)." Hazard Evaluation Division, Office of Pesticide Programs, USEPA. 2 pp.

Hoosfall, J.G. (1956). Principles of Fungicidal Action. Chronica Co., Waltham, Mass.

Hummel, Susan V. (August 15, 1989). "Revised Dietary Exposure to Maneb and ETU (Pennwalt). " Hazard Evaluation Division, Office of Pesticide Programs, USEPA. 24 pp.

Hummel, Susan V. (August 17, 1989). "Revised Dietary Exposure to Metiram and ETU." Hazard Evaluation Division, Office of Pesticide Programs, USEPA. 21 pp.

Hummel, Susan V. (August 17, 1989). "Revised Dietary Exposure to Mancozeb and ETU." Hazard Evaluation Division, Office of Pesticide Programs, USEPA. 22 pp.

Hummel, Susan V. (July 13, 1988). " Mancozeb-Registrant Response to Agency PD-1." Hazard Evaluation Division, Office of Pesticide Programs, USEPA. 25 pp. Attachments (4).

Hunter, B. et al. (1979). "Metiram tumorigenicity to mice in long term dietary administration for 13 weeks followed by a 6 week withdrawal period. (Unpublished study No. BSF/197/77612 by Huntingdon Research Centre, submitted by FMC Corp., Philadelphia, PA; EPA Accession No. 242192. MRID NO. 00330245.

Hunter, B. et al. (1981). "Metiram toxicity and tumorigenicity in prolonged dietary administration to the rat." (Unpublished study No. BSF/199/80391 by Huntingdon Researcy Centre, submitted by FMC Corp., Philadelphia, PA; EPA Accession Nos. 247209 - 247213.

Innes, J.R.M. et al. (1969). "Bioassay of Pesticides and Industrial Chemicals for Tumorigenicity in Mice: A Preliminary Note", 42, Journal of the National Cancer Institute 1101.

Iverson, F., K.S. Khera, and S.L. Hierlihy. (1980). "In vivo and in vitro Metabolism of Ethylenethiourea in the Rat and Cat. Toxic. and Appl. Pharm. 52:16-21.

Jablonicka, Angelika et al. (1989). "Analysis of chromosome abberations and sister-chromosome exchanges in peripheral blood lymphocytes of workers with occupational exposure to the mancozeb-containing fungicide Novozir Mn80. Mutation Research, 224, 143-146.

Just, Richard E., Darrell L. Hueth, and Mark Phillips. (1987). Benefits Estimates for Maneb. College Park, MD.

Kato, Y., Y. Odanaka,and O. Matano. (1976). "Metabolic Fate of Ethylenethiourea in Pregnant Rats", Bull. Environ. Contamin. Toxicol. 16(5): 546-555.

Khera, K.S. (1973). "Ethylenethiourea: Teratogenicity Study in Rats and Rabbits." Teratology 7:243-252.

Kocialski, Albin B. (September 21, 1989). "Establishment of an In Vivo Metabolic Conversion Factor of 7.5% for all Ethylene Bis (dithio) Carbamates (EBDCS) When Converting EBDCs to Ethylene Thiourea (ETU) In Vivo and Recalculations of the Previously Considered 20% In Vivo Conversion/Exposure Factor for EBDCs to ETU." Health Effects Division, Office of Pesticide Programs, USEPA. 2 pp plus attachments.

Kovacs, Martin, (January 21, 1987). "Maneb Frozen Storage Stability/Request for Time Extension." Hazard Evaluation Division, Office of Pesticide Programs, USEPA. 5 pp.

Kurtz and Bode (1985). "Application Exposure to the Home Gardener American Chemical Society Symposium Series No. 273."

Levy, Richard. (September, 1989). "Ethylene thioureau (ETU) Preliminary Qualitative Risk Assessment from an NTP 2-Year Rat and Mouse Chronic Oncogenicity Oral Feeding Study." Health Effects Division, Office of Pesticide Programs, USEPA. 25 pp.

Levy, Richard, and Hugh Pettigrew. (October 30, 1989). "Ethlyene thiourea [ETU] - Preliminary Qualitative Risk Assessment from an NTP 2-Year Rat and Mouse Chronic Oncogenicity Oral Feeding Study." Health Effects Division, Office of Pesticide Programs, USEPA. 27pp.

Lunchick, Curt. (October 15, 1987). "Review of Chemical Manufacturers Association DCI Rebuttal." Health Effects Division, Office of Pesticide Programs, USEPA, 6 pp.

Lunchick, Curt. (1989). "The Environmental Protection Agency's Use of Biological Monitoring Data for the Special Review of Alachlor." American Chemical Society Symposium Series #382.

Lunchick, Curt. (May 16, 1988). Review of Chevron Chemical Company submission (Accession Number 40504827). "Potential Exposure to Acephate During Home Use of Orthene Systemic Insect Control." 7 pp.

Lunchick, Curt. (December 16, 1988). "Dermal Exposure to Individuals Adding Nabam to Drilling Fluids by Open Pour - Request for Data." Health Effects Division, Office of Pesticide Programs, USEPA. 1 pp.

Lunchick, Curt. (August 16, 1988). "Nondietary Exposure to Metiram, Zineb, Mancozeb and Maneb Applied to Commercial Ornamentals and Homeowner Gardens." Hazard Evaluation Division Office of Pesticide Programs, USEPA. 10 pp.

Lunchick, Curt. (June 22, 1988). "Inhalation Exposure to Nabam Containing Microbiocides During Open Pouring." Hazard Evaluation Division, Office of Pesticide Programs, USEPA. 2pp.

Lunchick, Curt. (July 5, 1988). "Nondietary Exposure to Zineb, Mancozeb, and Maneb Applied to Sweet Corn, Grapes and Citrus." Hazard Evaluation Division, Office of Pesticide Programs, USEPA. 12 pp.

Lyman, W.R and R. J. Lacoste. (1971). "The Metabolic Fate of Dithane M-45 (Mancozeb)." Pesticide Terminal Residues. ed. A.S. Tahou. Invited Papers from the International Symposium on Pesticide Terminal Residues, Butterworths, London.

Maddy and Fong. (April 28, 1983). "Monitoring Worker Exposure to Dinoseb." California Department of Food and Agriculture, Report HS-1079.

Maitlen, J. C. et. al., (1986). "Workers in the Agricultural Environment: Dermal Exposure to Carbaryl." Pesticide Residues and Exposure, American Chemical Society, pp 83-103.

McGrew, G.T. (September 25, 1978). Alco Chemical Corporation. Philadelphia, PA. Personal communication to E.N. Pelletier EPA, Washington, D.C.

O'Hara, G.P. and L. J. DiDonato (February 18, 1985). "Dithane M-45 and Ethylenethiourea (ETU) 3 Month Dietary Study in Mice." Report No. 80R-124. Acc.# 259888.

Pelletier, E. Neil. (July 18, 1988). "Application Practices for Non-Agricultural Uses of Nabam Relative to Worker Exposure." Benefits and Use Division, Office of Pesticide Programs, USEPA. 3 pp.

Pelletier, E. Neil. (1982). "Memorandum to Captan RPAR RM entitled Final Use Practices Report Relative to Application and Exposure," dated April 9, 1982.

Phillips, W.P., and M. D. Grady (April, 1977). "Effects of Food Processing on Residues of Two Ethylenebisdithiocarbamate (EBDC) Fungicides and Ethylenethiourea (ETU)", EPA-600/1-77-021.

Richardson, Lionel A. EPA Contract Officer. (1978). "Evaluation of the EBDC Fungicides, Final Report." MRI Report. Done under contract to EPA, EPA Contract No. 68-01-4198, MRI Project No. 4307, RvR Consultants Project No. 91.

Rinde, Ester. (August 10, 1989) "Preliminarty Peer Review of Ethylene Thiourea." Health Effects Branch, Office of Pesticide Programs, USEPA. 42 pp.

Rispin, Amy S. (August 26, 1988). "Dietary and Nondietary Risk Assessment for EBDCs." Environmental Fate and Effects Division, Office of Pesticide Programs, USEPA. 6 pp. Attachments (10)

Ruddick, J. A., and K. S. Khera. (1975). "Pattern of Anomalies Following Single Oral Dose of Ethylene thiourea to Pregnant Rats", Teratology 12(3): 277-281.

Seidler, H., M. Hartig, W. Schnaak, and R. Engst. (1970). "Studies on the Metabolism of Certain Insecticides and Fungicides in the Rat - Distribution and Degradation of MC labeled Maneb." Nahrung. 14(5):3263-373.

Shema, B.G. (September 20, 1978). Betz Laboratories, Ind. Trevose PA. Personal Communication to E.N. Pelletier, EPA. Washington, D.C.

Smith, D.M. (1984). "Ethylenethiourea: thyroid function in two groups of exposed workers." British Journal of Industrial Medicine. 41:362-366.

Stevens, E.R., and Davis , J.E. (1980). "Potential Exposure of Workers During Potato Seed Piece Treatment with Captan." Bull. Environ. Contam. Toxicol., in press.

Tomerlin, Robert J. (September 21, 1989). "Revised EBDC/ETU Risk Assessment Using Recent Per Cent of Crop Treated Data." Hazard Evaluation Division, Office of Pesticide Programs, USEPA. 20 pp.

Tomerlin, Robert J. (December 9, 1988). "Captan Dietary Exposure Analysis and Oncogenic Risk Assessment." Hazard Evaluation Division, Office of Pesticide Programs, USEPA. 4 pp. Attachments (11 pp.).

Tomerlin, Robert J. and Susan L. Stanton. (July 7, 1988). "Dietary Exposure Analyses for Nabam Derived Ethylenethiourea: Chronic and Acute Exposure." Hazard Evaulation Division, Office of Pesticide Programs, USEPA. 4 pp. Attachments (3 pp.).

Tomerlin, Robert J. (July 15, 1988). "Chronic Dietary Exposure Analysis of Mancozeb and Mancozeb Derived Ethylenethiourea." Hazard Evaluation Division, Office of Pesticide Programs, USEPA. 6 pp. Attachments (16 pp).

Tomerlin, Robert J. (July 11, 1988). "Chronic Dietary Exposure Analysis of Zineb and Zineb Derived Ethylenethiourea." Hazard Evaulation Division, Office of Pesticide Programs, USEPA. 8 pp. Attachments (24 pp).

Tomerlin, Robert J. (July 5, 1988). "Dietary Exposure Analysis of Maneb and Maneb Derived Ethylenethiourea." Hazard Evaulation Division, Office of Pesticide Programs, USEPA. 7 pp. Attachments (17 pp.).

Tomerlin, Robert J. (June 30, 1988). "Dietary Exposure Analysis of Metiram and Metiram Derived Ethylenethiourea." Hazard Evaluation Division, Office of Pesticide Programs, USEPA. 6 pp. Attachments (10 pp.).

Tomerlin, Robert J. (July 6, 1988). "Acute Dietary Exposure Analysis of Maneb Derived Ethylenethiourea." Hazard Evaluation Division, Office of Pesticide Programs, USEPA. 2 pp. Attachments (8 pp.).

Tomerlin, Robert J. (July 14, 1988). "Acute Dietary Exposure Analysis of Zineb Derived Ethylenethiourea." Hazard Evaluation Division, Office of Pesticide Programs, USEPA. 2 pp. Attachments (10 pp.).

Tomerlin, Robert J. (July 14, 1988). "Actue Dietary Exposure Analysis for Mancozeb Derived Ethylenethiourea." Hazard Evaluation Division, Office of Pesticide Programs, USEPA. 2 pp. Attachments (7 pp.).

Tomerlin, Robert J. (July 7, 1988). "Acute Dietary Exposure Analysis of Metiram Derived Ethylenethiourea." Hazard Evaluation Division, Office of Pesticide Programs, USEPA. 2 pp. Attachments (4 pp.).

Truhaut, R., M. Fujita, N.P. Lich, and M. Chaigneau. (1973) "Study of Metabolic Transformations of Zineb." C.R. Acad. Sci. Paris Ser. D. 276(2):229-233.

Ulland, B.M. et al. (1972) "Thyroid Cancer in Rats from Ethylene thiourea Intake." J. Nat. Cancer Inst. 49:583-84.

University of Georgia. (1988). Preliminary Benefit Analysis of Chlorothalonil, Benomyl, and EBDC Use on Peanuts for the United States. Experiment, GA.

USDA/State/EPA Assessment Team. (1978). Draft Assessment of Ethylenebisdithiocarbamate (EBDC) Fungicide Uses In Agriculture. Part II: An Analysis of Current EBDC Uses, Their Benefit, the Role of Alternatives, and Impacts to Agriculture from Changes in EBDC Use Patterns. UDSA and USEPA, Washington DC.

Environmental Protection Agency (June 7, 1979). "The Carcinogen Assessment Group's Risk Assessment on Ethylene bisdithiocarbamates (EBDC)."

USEPA. (1989). "Captan: Notice of Intent to Cancel Registrations Conclusion of Special Review."

USEPA. (1988a). Biological and Economic Analysis of Review Fungicides for Apples. USEPA/OPP/BEAD.

USEPA. (1988b). Biological and Economic Analysis of Review Fungicides for Bananas. USEPA/OPP/BEAD.

USEPA. (1988c). Biological and Economic Analysis of Review Fungicides for Carrots. USEPA/OPP/BEAD.

USEPA. (1988d). Biological and Economic Analysis of Review Fungicides for Celery. USEPA/OPP/BEAD.

USEPA. (1988e). Biological and Economic Analysis of Review Fungicides for Cherries. USEPA/OPP/BEAD.

USEPA. (1988f). Biological and Economic Analysis of Review Fungicides for Citrus. USEPA/OPP/BEAD.

USEPA. (1988g). Biological and Economic Analysis of Review Fungicides for Cole Crops. USEPA/OPP/BEAD.

USEPA. (1988h). Biological and Economic Analysis of Review Fungicides for Grapes. USEPA/OPP/BEAD.

USEPA. (1988i). Biological and Economic Analysis of Review Fungicides for Lettuce. USEPA/OPP/BEAD.

USEPA. (1988j). Biological and Economic Analysis of Review Fungicides for Mushrooms. USEPA/OPP/BEAD.

USEPA. (1988k). Biological and Economic Analysis of Review Fungicides for Onions. USEPA/OPP/BEAD.

USEPA. (1988l). Biological and Economic Analysis of Review Fungicides for Ornamentals. USEPA/OPP/BEAD.

USEPA. (1988m). Biological and Economic Analysis of Review Fungicides for Peaches/Nectarines. USEPA/OPP/BEAD.

USEPA. (1988n). Biological and Economic Analysis of Review Fungicides for Potatoes. USEPA/OPP/BEAD.

USEPA. (1988o). Biological and Economic Analysis of Review Fungicides for Small Grains. USEPA/OPP/BEAD.

USEPA. (1988p). Biological and Economic Analysis of Review Fungicides for Spinach. USEPA/OPP/BEAD.

USEPA. (1988q). Biological and Economic Analysis of Review Fungicides for Sweet Corn. USEPA/OPP/BEAD.

USEPA. (1988r). Biological and Economic Analysis of Review Fungicides for Tomatoes. USEPA/OPP/BEAD.

USEPA. (1988s). Biological and Economic Analysis of Review Fungicides for Turf. USEPA/OPP/BEAD.

USEPA and USDA. (1979). Economic Impact Analysis of Cancelling the EBDC Fungicides. USEPA and USDA, Washington, DC.

USEPA. (1987). Guidance for the Reregistration of Pesticide Products Containing Mancozeb as the Active Ingredient.

Vonk, J.W. and A.K. Sijpesteijn. (1971). Tentative Identification of 2-imidazoline as a Transformation Product of Ethylene bisdithiocarbamate Fungicides. Pest. Biochem. Phys.

Watts, R.R., R. W. Storherr and H.H. Onley. (1974). "Effects of Cooking on Ethylenebisdithiocarbamate Degradation to Ethylenethiourea. Bull. Environ. Contam. Toxicol. 12(2): 12(2): 224-226.

Williams, W.M., P.W. Holden, D.W. Parsons, M.N. Lorber. (1988). Pesticides in Ground Water Data Base: 1988 Interim Report. Environmental Fate and Effects Division, USEPA.

Zogorski, W.J., and Lafferty, J.J. (1985). Karathane California Exposure Study, Rohm and Haas Company Technical Report No. 31L-85-01, 14 Feb. 1985.